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All-healing weapon: the value of *Oplopanax horridus* root bark in the treatment of type 2 diabetes

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All-healing weapon: the value of *Oplopanax horridus* root bark in the treatment of type 2 diabetes

By

Alissa Bronwyn Daschbach

Accepted in Partial Completion
of the Requirements for the Degree
Master of Arts

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Alissa Bronwyn Daschbach

June 04, 2019

All-healing weapon: the value of *Oplapanax horridus* root bark in the treatment of type 2 diabetes

A Thesis
Presented to
The Faculty of
Western Washington University

In Partial Fulfillment
Of the Requirements for the Degree
Master of Arts

by
Alissa Bronwyn Daschbach
June 2019

Abstract

While Indigenous Peoples live in an incredibly diverse geographical array with significant differences in language, culture, and history, there is a shared experience of an increased prevalence of type 2 diabetes and impaired glucose tolerance as compared to the dominant or colonizer populations. Indigenous patients with type 2 diabetes face multiple barriers to disease self-management: poverty, chronic stress, cultural oppression, limited access to healthy food or exercise, inadequate housing and limited resources to pay for medications. Epidemiological models of type 2 diabetes disregard the social determinants that play a prominent role in the disease's predominance among the world's Indigenous Peoples, creating a chasm between health care providers and the sick. This division can be reconciled through the recognition of cultural and spiritual connotations in disease management and the incorporation of sacred foods and medicinal plants in diabetes treatment care programs. For millennia, Indigenous Peoples of the Pacific Northwest have administered the inner bark of the stalk and roots of *Oplopanax horridus* (devil's-club) to treat illness and disease; including difficult childbirth, skin infections, cancer, lung hemorrhages, tuberculosis, and diabetes. Devil's-club is mentioned in written records of oral traditions and ethnographies, confirming the presence of this plant as a powerful symbol of medicine. These oral traditions, rooted in the culture for hundreds of years, serve as testimonies that speak to the sacred and medicinal value of this plant. The antidiabetic capability of this prickly shrub has been the object of Western pharmacological inquiry since 1938 when scientists recorded the extract to effect hypoglycemia in rabbits, validating the use of devil's-club tea to remedy symptoms of diabetes. These findings propelled my independent research in which I gathered and prepared the root bark to be extracted and tested against hyperglycemia *in vitro* by conducting a series of tests, especially focusing on the extracts' activity with the digestive enzymes that break down carbohydrates into the simple sugars used by the body for energy. By synthesizing a discussion of Indigenous Knowledge systems, ethnopharmacological inquiry, and biochemical analysis, I will demonstrate that the inner bark of *Oplopanax horridus* (devil's-club) contains antidiabetic activity as affirmed by oral testimonies of Pacific Northwest Indigenous Peoples.

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Hla Win-Piazza

Kathleen Young

My family.

Exact Scientific

Department of Natural Resources

Whatcom Chief

I think over again my small adventures,
My fears,
Those small ones that seemed so big,
For all the vital things
I had to get and to reach;
And yet there is only one great thing,
The only thing,
To live to see the great day that dawns
And the light that fills the world.

Anonymous (Inuit, 19th century)

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All-healing weapon: the value of *Oplopanax horridus* root bark in the treatment of type 2 diabetes



Oplopanax horridus

Preface

According to Fred Kelly (Anishinaabe Elder, Truth, and Reconciliation Commission of Canada, 2015):

“To take the territorial lands away from a people whose very spirit is so intrinsically connected to Mother Earth was to actually dispossess them of their very soul and being; it was to destroy whole Indigenous nations. Weakened by disease and separated from their traditional foods and medicines, First Nations Peoples had no defense against further government encroachments on their lives.” (Bagelman, Devereaux, & Hartley, 2016, p. 7).

Type 2 Diabetes is disproportionately suffered by the poor and Indigenous peoples of this world, a legacy of the colonizing health practices of governing bodies. Throughout the past two centuries, the United States and Canada followed the policy of treaties and reservations, which severed the long-lasting relationship between the First Nations and land, food, and medicine (Bagelman, Devereaux, & Hartley, 2016). Before the 1940s, diabetes was uncommon among Indigenous communities in the north Pacific coast of the United States and Canada (Körn & Ryser, 2009). Today, in Canada, the rate of diabetes among the Indigenous populations is three to five times higher than the general population. Canadian First Nations also develop diabetes at a younger age, experience the onset and severity of complications sooner, and have restricted access to adequate treatment and healthcare facilities (Maar, Manitowabi, Gzik, Mcgregor, &

Corbiere, 2011). Concurrently, in the United States, the prevalence of diabetes among AI/AN (American Indian/Alaska Native) is the highest at 15.3% among females and 14.9% for males (CDC, 2017).

A common thread in the determinants that interfere with the ability of Indigenous Peoples to recover and effectively treat diabetes are multiple barriers to treatment and self-management practices. These barriers include language, health literacy, cultural continuity, food insecurity, and physical inactivity due to limited access to exercise facilities and an inhospitable outdoors environment. Further systemic barriers include mental health and addiction issues that arise from multigenerational trauma resulting from colonial practices based on systemic structural violence (Davis, 2013). An essential step in healing these recurring wounds caused by structural violence is government health agencies supporting the revitalization of traditional food and medicinal systems, as opposed to treating Indigenous People with type 2 diabetes as research subjects solely using Western biomedical models.

Ten years ago, I wrote a paper titled “Diabetes and the Soul Wound” in which I countered the thrifty gene hypothesis as the reason behind the prevalence of type II diabetes in Indigenous Peoples worldwide. I realized through reading accounts of Indigenous scholars and tribal members that intergenerational trauma stemming from displacement from land resources, nutritionally valueless food rations, and violence committed in boarding schools led to the disease taking hold specifically in Native American populations. Beyond the disproportionately high rate of diabetes, those with the disease also suffered a higher rate of attendant morbid and mortal complications, including blindness, heart disease, and amputations. As an undergraduate, I explored the scientific fields of biological anthropology, biology, biochemistry, organic

chemistry, and ethnobotany; my primary focus was to understand why a disease is prevalent in specific populations and to search for a way to lower the rate of disease with medicinal treatment. These studies propelled me to look deeply into the pathogenesis of type 2 diabetes mellitus and try to find a pathway in medicine that reverses the complications. From this background, I built my current research program, working to draw a thread of connectivity between all these fields through the lens of a single thorny plant, *Oplopanax horridus* or devil's-club.

In this pursuit, I now see that despite purporting to honor those who passed this knowledge to me through the writings of Indigenous medicinal practitioners, personal testimonies, ethnobotanists, ethnographers, and anthropologists-- I am guilty of seeking personal gain through the research of *Oplopanax horridus*. I say these words because in the past five years of investigating whether this plant can treat diabetes my primary aim was to "discover" an active component to be utilized by pharma as a new diabetic medication. This personal quest was individualistic, and I realized that in my research I was appropriating Indigenous knowledge to support my hypothesis that the root bark of devil's-club contains an anti-hyperglycemic component. Thus, I state that any data revealing the anti-diabetic activity contained in this plant has been no discovery on my part. This activity is a reflection of the medicinal knowledge held by the Indigenous Peoples of the Pacific Northwest who have studied and used this plant for millennia.

Introduction

“Our stories tell of the plants and their supernatural properties; the importance of plants as a source of food, medicine, fibre, and wood; and of how to use them as cleansers and in spiritual ways. Today, we still use the names created and taught by our ancestors. These names and the knowledge of the plants are a vital part of our language.” (2013, p. 1)

Barbara Wilson (Kii'iljuus) *Xaaydaga* (Haida) Nation

Oplopanax horridus

Devil's-club, *Oplopanax horridus*, has a magnificent presence. Heavily armed with needle-like spines along its stalks and leaves, *O. horridus* presents a formidable display of protection and potency as it spreads in groves throughout the lowland forest areas of the Pacific Northwest Coast. The medicinal capability of this prickly shrub is just as magnificent as its presence. The name *Oplopanax* is a compound word stemming from the Greek *όπλο* or *oplo*-weapon and the Latin *panax*- (*panacea*) all-healing. All-healing weapon. For millennia, Indigenous Peoples of this region have administered the inner bark of the stalk and roots of devil's-club to treat illness and disease; including difficult childbirth, skin infections, cancer, lung hemorrhages, tuberculosis, and diabetes (Calway, et al., 2012; Compton, 1993; Turner, 1982). Over 38 linguistic groups use devil's-club for the treatment of at least 34 different medical conditions throughout coastal British Columbia and Washington state (Turner, 1982). Of these 38 groups, thirteen (Cree, Haida, Halkomelem, Heiltsuk, Metis, Nlaka'pamux, Nuxalk, Sechelt, Secwepemc, Squamish, Stl'atl'imx, Straits Salish and Tsimshian) use the root bark to treat diabetes, yet this activity has not been proven in pharmacological studies (Johnson-Gottesfield, 1992; Justice, 1966; Lantz, Turner & Swerhun, 2004; Large & Brocklesby, 1938; Smith G. W., 1973; Turner, 1982).

The antidiabetic capability of this prickly shrub has been the object of Western pharmacological inquiry since research scientists Brockelsby and Large (1938) conducted an experiment with rabbits to verify the presence of a hypoglycemic substance in the root bark of devil's-club. This study claimed that the rabbits who ingested the extract showed marked hypoglycemia in blood. In the 1940s, scientists tried to reproduce these results with standardized extracts only to obtain negative results of the hypoglycemic effect (Piccoli, 1940; Stuhr & Henry, 1944). Dr. Thommasen et al. (1990) refuted Brockelsby and Large's study when they tested the extract in two diabetic human subjects who did not develop hypoglycemia (Thommasen, Wilson & McIlwain). Further research conducted by the Yuan group (2011) of the University of Chicago also contradicted the 1938 study in which glycoside active constituents isolated from OH extract showed no inhibitory activity against α -amylase, the digestive enzyme responsible for breaking down large sugar molecules into glucose (Huang W.-H., Zhang, Meng, Yuan, & Li). Despite the contradictory evidence, there are multiple ethnographic sources that reference the use of the extract of *O. horridus* in the treatment of diabetic symptoms by individuals in the Pacific Northwest region (Johnson L. M., 2006; Justice, 1966; Thommasen, Loewen & McInnes, 1995; Turner & Hebda, 1990; Turner, Thompson, et al., 1990).

Anthropologists and ethnobotanists, including Boas, Garfield, Emmons, Gunther, Smith, Lantz, Johnson, and Turner, have written of the multitude of uses of devil's-club, spanning from ingesting the inner root extract to treat deadly diseases like tuberculosis and cancer to ceremonial imbibement to elicit protection from spiritual adversaries. Written records of oral traditions and ethnographies mention devil's-club where the plant serves as a powerful symbol of medicine and sacredness (Boas & Tate, 1916; Boas, 1930; Smith G. W., 1973; Krause, 1956;

Ryan, 1952; Thie, 1999). These oral traditions, rooted in Northwest Coast Indigenous cultures for hundreds of years, are testimonies that speak of the value of this plant and describe ceremonies that are honored and sacred traditions. These narratives tell of the longtime usage of devil's-club as medicine and to enhance the shaman's spiritual experience. Shamans used the root bark in ceremonies, fasting for several days while drinking only a concoction of the bark, inducing a heightened spiritual state that mimicked symptoms of hypoglycemia (Boas & Tate, 1916; Boas, 1923; Krause, 1956).

These findings directed my independent research in which I gathered and prepared the root bark to be extracted and tested against hyperglycemia *in vitro*. Not to be deterred by earlier studies that denied the anti-diabetic properties of the plant, I conducted a series of tests to determine if the plant contained components that could treat diabetic symptoms (no rabbits involved). These phytochemical tests were based on measuring two possible activities of the root bark extract; one being antioxidant against reactive oxygen species and the other being inhibitory against the digestive enzymes that break down carbohydrates into simple sugars. Evidence from these tests bared three findings. The first test showed that the root bark contains polyphenols, chemical compounds known to act as an antioxidant and reduce inflammation within the human body. The second and third tests revealed that the extracts of the inner root bark inhibit the activity of α -amylase and α -glucosidase, the pancreatic and intestinal digestive enzymes responsible for the breakdown of long simple sugars, or carbohydrates, after being ingested. These results are particularly promising when considering that the lowering of postprandial hyperglycemia in people with type 2 diabetes lowers the risk for the development of cardiovascular disease among other macro- and microvascular

complications. Evidence from the activity of the root bark extract to inhibit digestive enzymes shows the power of the plant to protect against type 2 diabetes. Further research to elucidate the compound or compounds responsible for this activity may lead to a new oral hypoglycemic agent that can ameliorate the morbid complications suffered by the millions who have diabetes today. By weaving a discussion of the oral narratives belonging to the Indigenous Peoples of the Pacific Northwest, literature review, and the biochemical analyses of the root bark I conducted at Western Washington University, I will explain why *Oplopanax horridus* (OH) has been and currently is administered to treat diabetes despite scientific evidence to the contrary.

Definitions: Indigenous Peoples, Traditional Ecological Knowledge, Indigenous Knowledge Systems, Social Determinants of Health

Indigenous Peoples

In this work, Indigenous Peoples are referenced using the following definitions by the United Nations and Dr. Lori Lambert. In the 2007 United Nations Declaration on the rights of Indigenous Peoples, the working definition of Indigenous peoples is:

Indigenous communities, peoples, and nations are those which, having a historical continuity with pre-invasion and pre-colonial societies that developed on their territories, consider themselves distinct from other sectors of society now prevailing in those territories, or parts of them. They form at present non-dominant sectors of society and are determined to preserve, develop and transmit to future generations their ancestral territories, and their ethnic identity, as the basis of their continued existence as peoples, in accordance with their own cultural patterns, social institutions, and legal systems. (2014, p. 6)

Indigenous people refer to those who are described by Dr. Lori Lambert (Mi'kmaq/Abenaki), founder of the American Indigenous Research Association:

Indigenous people are the tribal people in independent countries whose distinctive identity, values, and history distinguishes them from other sections of the national community. We are the descendants of the pre-colonial inhabitants of a geographical area and retain some or all of our cultural values, history, and lifeways, and, despite our legal status, retain some or all of our social, economic, cultural, and political institutions. (2014, p. 1)

Lambert advocates the decolonization of research methodologies that have historically exploited knowledge from Indigenous people without giving back to the communities from which they gained data or information. In decolonizing research, Lambert expresses the import of giving back to the community who gifted the knowledge that advanced research in a manner that considers the needs of and shares the benefits with Indigenous participants. According to Lambert, decolonizing research involves research that moves the community forward through positive and strengthening research questions with no harm to culture, language, or individuals nor exploitation of the research data itself.

Traditional Ecological Knowledge

The term Traditional Ecological Knowledge (TEK) has been under scrutiny by Indigenous educators, members, and activists as many scholars and scientists have coined the term and defined it in the form of cultural and intellectual appropriation that modifies Indigenous knowledge to fit Western scientific frameworks (Kim, Asghar & Jordan, 2017; Simpson, 2004). Simpson (2004) argues that some Western research scientists will appropriate knowledge gained from Indigenous sources and name it TEK, using the knowledge as baseline data because their scientific research is weak and wish to exert greater control over the environments and utilize natural resources in Indigenous territories. Simpson further holds that “the spiritual foundations of IK [Indigenous Knowledge] and the Indigenous values and worldviews that

support it are of less interest often because they exist in opposition to the worldview and values of the dominating societies” (p. 374). In medicine, research scientists will interview local experts of plants to find remedies, even cures, for disease without respecting or validating the spiritual framework from which the medicinal expertise grows. Beyond this ignorance of the Indigenous values held within this knowledge, researchers will occupy these communities, picking pieces of knowledge and gathering plant specimens and leave these places without compensating those who gifted the knowledge in the first place.

Ignace, Ignace, and Turner (2016) wrote of systems of traditional ecological knowledge and wisdom in which the traditions of knowledge are not stagnant pieces of information waiting to be properly examined by Western science. According to Ignace, Ignace, and Turner, these traditions “are not frozen to the past but connect to Indigenous peoples’ continuing existence, rights, and interests in sustainable ecologies of their homelands; the narrative of traditions is seen as guiding the path for present and future actions.” (p. 408). In this work, when using the terms “traditional,” “Traditional Knowledge,” or any knowledge sourced in Indigenous knowledge systems, I refer to the term legally defined by the Sitka Tribe of Alaska in the Ordinance Governing Kayaani Commission and Traditional Plant Gathering Guidelines:

The term ‘Traditional Knowledge’ refers to the traditional spiritual methods, means and ways of gathering, processing, utilizing and protecting traditional plants that is the exclusive property of Sitka Tribal citizens as a result of the intimate association that their ancestors fostered with their traditional territory and all of the marine, land, animal and plant life that naturally occurs with this territory. This intimate knowledge has been handed down since time immemorial and today is in the hands of tribal Elders who wish to protect and preserve this knowledge for the next generation (2003, p. 3).

Indigenous Knowledge Systems

Indigenous knowledge systems, or Indigenous science, are defined by a body of traditional, environmental and cultural knowledge that serve to sustain a unique people throughout generations of living within a distinct ecological region (Cajete, 2014, p. 110). Indigenous scientific knowledge follows closely in methods with contemporary Western science. Both share a path of using classification, inference, questioning, observation, interpretation, prediction, problem-solving, and adaptation to reach conclusions. Indigenous science differs in Western science contextually in that:

Western science perceives from a 'low-context' view, reducing context to a minimum. Indigenous science may be defined as a 'multi-contextual system of thought, action, and orientation applied by an Indigenous people through which they interpret how Nature works in 'their place.' Indigenous knowledge may be defined as a 'high-context' body of knowledge built up over generations by culturally distinct people living in close contact with a 'place,' its plants, animals, waters, mountains, deserts, plains, etc. Epistemological characteristics of Indigenous science include oral transmission; observation over generations; cyclical time orientation; quantification is a macro level; specific cultural/literal style and symbolism; knowledge is contexted to a specific tribal culture and place; conservation of knowledge through time and generations. (Cajete, 2014: p. 113)

Drawing from the theories and thought experiments of European scientists like Bacon, Galileo, Newton, and Einstein, Western science, with its basis in objective conclusions and the scientific method developed into a body of knowledge independent and distinct from Indigenous knowledge systems. Being based on experiments and empirical data that can be corrected to make new data, Western science is framed by a system in which scientific theories are falsifiable and able to be tested (Lynne, 2015). This objective perspective has been used to present Western science as superior to all other forms of knowledge. However, the questions asked and investigations that follow are culturally mediated, a reflection of the society,

language, and value system of the scientist who asks the question (Peat, 2014). Thus, culture cannot be separated from science, no matter how empirically motivated the theory and experiment. In this thesis, I will be drawing from both fields of science to explain why devil's-club serves to treat Indigenous patients with type 2 diabetes from a holistic perspective.

Social Determinants of Health

The World Health Organization (2019) defines social determinants of health (SDH) as:

The conditions in which people are born, grow, work, live, and age, and the wider set of forces and systems shaping the conditions of daily life. These forces and systems include economic policies and systems, development agendas, social norms, social policies, and political systems.

In the determinants of health model, political, economic, and social structures can facilitate or impede access to the resources that maintain health and provide treatment to illness disease. Social determinants greatly influence the health of Indigenous peoples.

In her article titled "Structural Determinants of Aboriginal Health," Charlotte Reading (2015) offers an Indigenous paradigm to explain the social determinants of health using the metaphor of a tree. Using the crown (leaves and branches), trunk, and roots as an analogy, Reading writes of the proximal, intermediate, and distal determinants of health as interrelated elements that influence the health of the Indigenous Peoples of the world. Proximal determinants-- the leaves and branches of the tree--are factors that touch an individual's life directly: early child development, income, and social status, education and literacy, social support networks, employment,

working conditions, the physical environment, gender, and culture. Poverty, unemployment, discrimination, and lack of education are all determinants that are considerable obstacles to a healthy life in this domain. Reading identifies the intermediate determinants--the trunk of the tree--in social structures like the government, health care systems, and education. These structures can relieve stressors caused by proximal influences and protect health and can also significantly hinder health. In the Indigenous model of health, intermediate determinants include family and kinship networks, relationship to language, ceremonies, the land, and the sharing of Indigenous ways of knowing. Any removal or government-directed control of these resources in Indigenous communities leads to poorer health outcomes. Lastly, Reading identifies the distal determinants--the roots of the tree--as the embedded structural foundations (historical, ideological, economic, social) within a society that influence the health of Indigenous peoples in an all-encompassing manner. These foundations also embody Indigenous world views, spirituality, and self-determination. Any decay in these foundations touches the proximal and intermediate determinants of health resulting in inequity and disparities in health.

Type 2 Diabetes and Indigenous Peoples

Indigenous populations worldwide live with social, cultural, demographic, psycho-emotional, and nutritional changes that have a lasting impact on health (Valeggia & Snodgrass, 2015, p. 118). These interruptions have occurred in separate places in time and space. Some lives were negatively transformed due to colonization centuries ago, while others are experiencing the effects of globalization and the commercialization of food and lifestyles in the

present. An estimated 400 million individuals of 5000 different Indigenous Peoples live in more than 70 countries throughout the world from the Arctic to the South Pacific (Corntassel & Bryce, 2012; Ferreira & Lang, 2006; Vallengia & Snodgrass, 2015). Kim TallBear (2013), a Sisseton Wahpeton Oyate professor of Native Studies at the University of Alberta, speaks of Indigenous Peoples as “biological, cultural, and political groupings constituted in dynamic, long-standing relationships with each other and with living landscapes that define their people-specific identities and, more broadly, their indigeneity” (p. 510). While Indigenous people live in an incredibly diverse geographical array with major differences in language, culture, and history; there is a shared experience of an increased prevalence of type 2 diabetes and impaired glucose tolerance when compared to the local dominant or colonizer populations (Dussart, 2010; Ferreira & Lang, 2006; Yu & Zinman, 2007, p. 159). Indigenous people with type 2 diabetes face multiple barriers to disease management such as poverty, chronic stress, and cultural oppression. Social determinants of health contribute to the increased diabetes prevalence as excessive stress stemming from limited access to healthy food or exercise, inadequate housing, and limited resources to pay for medications interfere with self-management of the disease (Crowshoe, et al. 2018; Sittner, Greenfield & Walls, 2018).

In North America, Indigenous Peoples have the highest rate of type 2 diabetes in all groups. In Canada, the prevalence of type 2 diabetes is 3 to 5 times higher in Indigenous populations than in the general population (Crowshoe, et al., 2018). In the United States, Indigenous Peoples are two times more likely to have type 2 diabetes and die from diabetic complications than Caucasians. Colonial policies that have directly contributed to the high prevalence of diabetes in Indigenous populations are land dispossession, residential schooling

systems, and the lack of access to traditional foods (Freeman, 2017). The process of colonization in the 20th century involved separating children from family through placement in residential schools. The government supported residential school programs in the United States and Canada denied the school children access to their traditional diet and they were fed nutritionally valueless foods from which many suffered from malnutrition and starvation (Bagelman, Devereaux, & Hartley, 2016). Currently, the pollution and contamination of water sources and soil coupled with private enterprise occupying hunting and fishing lands severely impede the ability of Indigenous communities to continue eating nutrient- and protein-rich local foods (Boxberger, 2007; McAuley & Knopper, 2011; Schreiber, 2002; Willows, et al., 2018).

Canadian physicians working with Indigenous patients report the effects of colonization on health as historical changes in diet and unresolved grief from dislocation and residential schools. Crowshoe et al. (2018) interviewed Canadian physicians and recorded their experiences with diabetes care for their Indigenous patients. Participants in the study cited culture being protective against diabetes, yet more often mentioned were the barriers to disease management that shaped the health outcomes of their patients. Western epidemiological models of diabetes disregard external factors that play a prominent role in its predominance, and in this disregard is set a chasm between health care providers and the sick. This division can be reconciled through the recognition of cultural and spiritual connotations in disease management and the incorporation of sacred foods and medicinal plants in diabetes treatment care programs.

Biological and Social Determinants of Type 2 Diabetes

Diabetes is a group of metabolic diseases characterized by abnormal fuel metabolism, insulin deficiency or dysfunction and hyperglycemia (high blood glucose or sugar)--a condition that can lead to serious complications and death if left untreated (Ortiz-Andrade, et al., 2007; Yki-Järvinen & McClain, 2015). In normal metabolism, the consumption of food stimulates the pancreas to secrete insulin, a hormone responsible for signaling protein receptors (GLUT 4) to carry glucose into the liver, muscles, and adipose tissues. Any disruption in this finely-tuned mechanism will cause glucose to remain in the blood, starving the cells of its primary energy source and leading to chronic hyperglycemia, or the diabetic condition.

Persistently elevated levels of glucose cause an accelerated loss of function of the insulin-producing β -cells due to a condition called glucose toxicity. Glucose toxicity occurs when high levels of glucose levels in pancreatic β -cells lead to an accelerated loss of insulin because of specific molecular mechanisms that affect gene expression and sensitivity of insulin in the early stages of type 1 and type 2 diabetes (Yki-Järvinen & McClain, 2015). In these cases, eating a meal will lead to elevated postprandial glucose levels and hyperglycemia. Without treatment, these high glucose levels wear on the human body as tissues that depend on glucose for energy production are starved of this crucial fuel. The disease progresses accompanied by severe complications (Shan, Li, Khamaisi, & Qiang, 2017). Macro- and microvascular complications that arise from prolonged hyperglycemia contribute to the high rate of loss of limbs and life in the many that suffer from the disease (Chan, 2015). Several epidemiological studies and clinical trials have shown that chronic hyperglycemia leads to coronary artery disease, renal failure, blindness, limb amputations, cerebrovascular disease, neurological complications and an early

death (Bell, 2001; Ceriello, et al., 2006; Grandl & Wolfum, 2018; NCD Risk Factor Collaboration, 2016; Flavio Silva, Mendes Ferreira, & de Pinho, 2017).

The two main classifications of diabetes are Type 1 and Type 2. Type 1 diabetes mellitus (T1DM) is a chronic inflammatory disease caused by cell-mediated destruction of the insulin-producing β -cells in the islet of Langerhans. The disease develops from a combination of genetic susceptibility and environmental factors. A person with type 1 diabetes depends on insulin to survive. Type 2 diabetes mellitus, T2DM, is a heterogeneous disorder stemming from abnormalities in insulin action and impaired insulin secretion. The β -cells in T2DM patients have both decreased mass and number of insulin secretory granules. Glucose toxicity, cell exposure to chronically high glucose levels, may cause the defect in insulin secretion. Other factors that accompany hyperglycemia in type 2 diabetics are hyperlipidemia, oxidative stress, and protein glycation (Rodrigues Franco, et al., 2018). Type 2 diabetes mellitus is a complex metabolic disorder that leads to cardiovascular disease along with many other pathophysiologic abnormalities (Muhammad Abdul-Ghani, 2015).

Carbohydrates are a favorite source of food in the human diet with starch and sucrose the primary forms of carbohydrates consumed. Carbohydrates are broken down in the mouth by digestive enzymes in saliva. This digestion continues in the small intestine where digestive enzymes break down the starch to form the glucose molecule. Glucose is then absorbed into the bloodstream through the intestinal walls. The α -amylase digestive enzyme found in saliva and pancreatic juices breaks down starch into an oligosaccharide (long chain sugar) or disaccharides (two sugars bonded together). α -Glucosidase, an enzyme bound in the epithelium of the small intestine, breaks these long-chain sugars into glucose. The hydrolysis of starch by

pancreatic α -amylase and the absorption of glucose in the small intestine by α -glucosidase cause a rapid rise in blood glucose levels, contributing to hyperglycemia in type 2 diabetes patients (Nguyen, Wang, & Nguyen, 2018).

Postprandial glucose (PPG), the level of glucose within 1-2 hours of eating, is a potent mediator of microvascular and macrovascular complications in type 2 diabetics with increased levels of PPG leading to increased risk of cardiovascular events (Bell, 2012; Mannucci, Monami, et al., 2012). A therapeutic approach to decrease postprandial hyperglycemia is to slow the absorption of glucose with a form of medicine that inhibits these digestive enzymes, thus decreasing exposure to high glucose concentrations and reversing its damaging effects. Oral hypoglycemic agents have been prescribed to type 2 diabetics to assist in the control of glucose levels. Of these, acarbose, miglitol, and voglibose are prescribed to control postprandial hyperglycemia. Acarbose is used to control postprandial hyperglycemia via inhibition of both α -amylase and α -glucosidase, digestive enzymes responsible for the breakdown of polysaccharides to monosaccharides. Research with acarbose shows that patients who take this inhibitor with insulin have improved oxidative stress levels and less systemic inflammation, allowing for a reduction in postprandial glucose levels and an improvement in diabetic complications (Li, Fu, et al., 2016). However, abdominal pain and diarrhea are irritating side effects that deflect patients from taking acarbose. The discovery of alternative medications with digestive enzyme inhibitory activity is a promising field of research in the quest for reducing morbidity and mortality in diabetic patients without uncomfortable side effects (Rodrigues Franco, et al., 2018).

Clinical research states that people with type 2 diabetes can live healthy, functional lives if they practice great care in the management of their glucose levels through their diet and practicing physical and stress-relieving activities (Hemmingsen, 2017). According to clinical practice guidelines, the management of this chronic disease requires the patient to intimately understand the nature of their disease and practice strict daily self-management practices to prevent or delay diabetic complications (Galaviz, et al., 2018; Gerich, 2003). In Indigenous populations, type 2 diabetes is the fourth cause of mortality with coronary artery disease, a common complication of type 2 diabetes, ranking as the number one cause of death (Espey, et al., 2014). Further, incident rates of end-stage kidney disease and amputations are many-fold higher in Indigenous populations as compared to non-Indigenous diabetics (Yu & Zinman, 2007). Social determinants create barriers for Indigenous peoples, interfering with their ability to manage the disease (Maar, et al., 2011).

The diabetes epidemic in Indigenous communities results from the interaction of intricate genetic and epigenetic systems within a complex social structure that encompasses a multitude of behavioral and environmental effects (Zimmet, 2014). The adoption of the dominating society's lifestyle, such as urbanization and Western diet, plays a prominent role in the development of type 2 diabetes in Indigenous populations. In the Indigenous model of disease, trauma, and stress stemming from poverty, microaggressions experienced in a healthcare setting, marginalization due to colonizing policies and practice (i.e. the violence of boarding schools and forced assimilation), and poverty lead to disease taking hold in Indigenous bodies (Sittner, Greenfield, & Walls, 2018). Microaggressions are a form of racial discrimination that is subtle and covert in nature, reflecting in slights, insults, and prejudices. Microaggressions

in the healthcare setting are positively associated with depressive symptoms that impact physical and mental health, creating a barrier in recovery and treatment of diabetes in Indigenous populations. Self-determination (“being a self-sufficient Nation), cultural continuity (“being who we are”), and cultural revitalization encourage positive mental health and self-care in these communities, attributes that protect people against disease and lead to recovery and healing (Oster, Grier, Lightening, Mayan, & Toth, 2014). Highlighting community and cultural strengths as opposed to focusing on the high rates of diabetes changes the approach to how to treat the disease. Despite the many barriers facing Indigenous peoples, the resilience and cultural strengths that these communities show reduce distress and allow for health to increase at a holistic level (Kading, et al., 2015).

Methodology, Objectives, and Significance of the Research Program

In exploring the antidiabetic capabilities of devil’s-club root bark, I followed an ethnopharmacological methodology to examine the plant and gain an understanding of its medicinal and culturally significant properties. The first step was to obtain an exact botanical identification of the plant by consulting a local herbal specialist on Lummi Island, Washington. I then conducted a thorough search of anthropological, chemical, and pharmacological literature to understand the physiological effects of the crude extracts of the plant. From this search, I recorded the known isolated chemical constituents of *O. horridus*. Lastly, I compared the medicinal effects known to bioscience with the data I obtained in the series of tests I conducted on the inner root bark of the stalks and roots of devil’s-club (Browner, Ortiz de Montellano, & Rubel, 1988). I used a multi-perspective approach to explain the mechanism of action of devil’s-club in diabetes, including references to the oral history and mythology and an in-depth

description of the cultural and medicinal values of devil's-club. A scientific methodology was used to explain the possible antidiabetic capabilities within the inner root bark through pharmacological tests and results along with the data I collected regarding phenolics quantity and inhibitory activity against the digestive enzymes, α -amylase and α -glucosidase.

The heart and guiding intention of this thesis is actively working to improve the state of the world in which the poor and marginalized-- the majority of whom belong to Indigenous communities-- are dying and morbidly sick from type 2 diabetes, a disease that can be successfully managed with careful self-management and effective healthcare resources. In Indigenous communities where culture is being protected through language, food, and medicine revitalization, the people are guarded against diabetes (Oster, Grier, Lightening, Mayan, & Toth, 2014). From this perspective, I introduce the first chapter with a discussion of the global epidemiology of type 2 diabetes, focusing on the burden carried by the world's Indigenous Peoples. Colonization and government federal policies that designed the reservation and boarding school systems continue to harm the health-- physical and mental-- of Indigenous communities in the United States and Canada. In this chapter, I argue that the decolonization of the diabetes health model and treatment plans through cultural continuity, revitalization, and self-determination practices serve to provide Indigenous patients with type 2 diabetes with the most effective strategy in management of the disease, healing, and recovery.

The focus of Chapter 2 is to provide the reader with a multidimensional background of devil's-club as well as to present a picture of the deep-rooted relationship between the Indigenous Peoples of the Pacific Northwest and this plant. I begin with a botanical description of *Oplopanax horridus* and continue with a discussion of the traditional use of the root bark

extract in medicinal practices. This chapter explores the oral records, lists observations by explorers, ethnographers, and ethnobotanists, and discusses personal and Indigenous testimonies about the plant. A thorough review of scientific studies, a description of the chemical background of the plant, and research studies are also presented in Chapter 2; along with a discussion of how scientific evidence supports the medicinal use of devil's-club extract as an effective treatment for serious diseases, including tuberculosis and cancer. Past studies of the extract of devil's-club tested on rabbits for hypoglycemic activity attest and deny the anti-diabetic activity. In this context, I will introduce the few studies that support the use of devil's-club extract for the treatment of diabetes.

The third chapter is devoted to a thorough description of type 2 diabetes with a focus into the pathophysiology, epidemiology, and conventional treatment schemes of the disease. Chapter 3 begins with a discussion of the physiology of insulin and its relationship with glucose metabolism and homeostasis. I continue with a description of the pathogenesis of the disease when this delicate system goes awry. I conclude the chapter with explaining why post-prandial hyperglycemia is responsible for the development of the morbid and mortal complications that accompany type 2 diabetes and how the development of new drugs that lower postprandial hyperglycemia is an important therapeutic approach to disease management.

Supportive studies show that medicinal use of devil's-club tea in Indigenous communities effectively treats serious diseases, including tuberculosis, cancer, and diabetes. In the fourth chapter, Methodology, I present the evidence from the experiments I conducted that supports these studies with a specific application in the treatment of diabetes. In this chapter, I explain the ethnopharmacological methodology used in the research of *Oplopanax horridus* and

discuss theoretical considerations, especially Indigenous research methods in harmony with the Western Scientific Method. Included in this chapter is the Methods section in which the extraction and bioassay methods I followed to test the root bark for antidiabetic activity are presented. The methods used to validate devil's-club tea as an effective diabetes treatment were conducted in the lab, using digestive enzyme inhibition bioassays, and quantification of polyphenol content. The Experimental section describes these three different bioassay explorations in which data confirms the antioxidant and digestive enzyme inhibitory activity of devil's-club. The results from experimentation on the root bark show that the extract inhibits the breakdown of carbohydrates due to its inhibitory activity against α -glucosidase and α -amylase. Other results show elevated levels polyphenols in the extracts, which are a potent class of antioxidants that have a protective action against the disease process that leads to type 2 diabetes.

My primary objective in this thesis is to approach an ethnopharmaceutical survey of devil's-club in a manner that honors Indigenous research agenda as to benefit the People who provided the deep living knowledge from the onset of my research. I will focus this objective on the theory presented by Linda Tuhiwai Smith (Ngati Awa and Ngati Porou, director of the International Research Institute for Maori and Indigenous Education at the University of Auckland), a world-renowned theorist on the decolonization of Indigenous Peoples. Smith has built a model called the Indigenous Research Agenda to shift research about Indigenous Peoples away from the dominant paradigm toward healing that is culturally-based and holistic in nature (Lucero, 2011). Current health programs fail to improve the health of Indigenous communities due to ignorance of the cultural, spiritual, and physical needs of diabetic patients.

Those programs that aim to connect with the community using restorative models based on healing intergenerational trauma and focusing on positive health through reconnection to the traditional foods, language, and family result in healthier clients. As explained by Smith, indigenous research agenda consists of four elements that focus on the goal of self-determination: healing, decolonization, transformation, and mobilization (Smith L. T., 2004). Devil's-club is a sacred plant that serves in all four elements of Smith's model of Indigenous self-determination in the treatment of type 2 diabetes.

Devil's-club is an extraordinary plant that serves as a cultural keystone species, a plant that is used to fulfill spiritual, medicinal, and technical needs in Indigenous Peoples of the Pacific Northwest. Oral traditions and individual testimonies confirm the long-time usage of the decoction of devil's-club in treating ailments, disease, and to enhance the shaman's spiritual experience. These stories are songs of the past that carry through to the present and stories that are held in the spirits and bodies of a People, to heal and preserve. Using the chemical exploration of the plant as a background to the beauty and scientific elegance of the interrelationship between a plant and its People, I will explain why the root bark of devil's-club is effective in the treatment of the symptoms of type 2 diabetes. Ethical considerations when looking into a sacred ceremonial plant are important and necessary. The ethnobotanical approach to pharmacological research in this study recognizes the intellectual property rights of the keepers of plant knowledge, assists local communities and the conservation of their resources and environments, and also ensures the equitable distribution of benefits obtained from the use of these resources (including genetic material or chemical structures) (McClatchey, Mahady, Bennett, Shielsa, & Savo, 2009). With these considerations, I will

synthesize a discussion of Indigenous knowledge systems, ethnopharmacological inquiry, and my own biochemical analyses to demonstrate that the inner bark of *Oplapanax horridus* (devil's-club) contains antidiabetic activity as affirmed by oral testimonies of Pacific Northwest Indigenous Peoples.

Chapter 1: Indigenous Peoples and the burden of type 2 diabetes

Globally, colonization and domination by outsiders have profoundly affected the health and livelihood of Indigenous populations to detrimental levels. The invasion and occupation of Indigenous territories caused displacement of entire communities, the suppression of the traditional diet, and a change from physically active to sedentary behavior due to land loss and inhospitable outdoor environments. These social determinants have contributed to the disproportionately high rate of type 2 diabetes prevalence among Indigenous communities, particularly within affluent nations such as the United States and Canada. The conventional treatment schemes for patients with type 2 diabetes has proven to be ineffective in treating Indigenous patients as they face multiple barriers that impede their ability to recover from the disease. In the following chapter, I will present the reader with an overview of the global epidemiology of the disease, describe the barriers to treatment for Indigenous patients caused by an inadequate treatment model, and conclude with the strategy for health and healing from the disease using an Indigenous health model based on cultural continuity and self-determination.

1.1 Global epidemiology of type 2 diabetes: Who carries the burden?

1.1.1 Global epidemic

Type 2 diabetes is a global epidemic, wreaking havoc on the health of hundreds of millions and causing an immense economic burden on the health systems that treat those ill from the disease. The number of people diagnosed with type 2 diabetes has doubled in the past 20 years, approaching 500 million worldwide with an expected growth rate reaching 642 million

by 2040 (IDF, 2017; Kaiser, Zhang & Van der Plujim, 2018; Roglic, 2016; Zimmet, Alberti, et al., 2016). In 2013, the global prevalence of diabetes was 8.3% among people aged 20-79 years and within the world's most populous countries, India and China, was between 9 and 10% (65 and 100 million, respectively) (Seuring, Archangelidi & Suhrcke, 2015). Diabetes and the complications that accompany the disease are major causes of early death in most countries. The World Health Organization (WHO) estimates that high blood glucose is the third highest risk factor for premature mortality globally, after high blood pressure and tobacco use. Many with diabetes live undiagnosed for long periods of time because there are few symptoms that point to the disease in the early years of its occurrence. The number of people who (46% of global cases are not diagnosed) have the disease is much higher than reported data due to the asymptomatic nature of the disease in its early stages (Galaviz, et al. 2018).

The International Diabetes Federation is a global organization consisting of professional and individual volunteers from 165 countries and territories with a primary mission of promoting diabetes care, prevention, and a cure worldwide. Every two years, IDF publishes the Diabetes Atlas to provide a resource on the global burden of diabetes that includes data on diabetes cases, prevalence, mortality and financial costs at global, regional, and national levels. The following statistics all follow from this publication in which the researchers responsible for data borrowed information from the United Nations population estimates, WHO healthcare expenditures and mortality rates, along with 221 data sources from 131 countries.

The International Diabetes Federation (IDF) considers type 2 diabetes to be one of the largest health emergencies of the 21st century. According to the IDF Atlas, one in eleven adults have diabetes, one in two adults with diabetes is undiagnosed, one in seven births is affected

by gestational diabetes, and 12% of global health expenditure is spent on diabetes (Cavan, et al., 2015). Mortality related to diabetes mellitus has increased from 2.0 million in the year 2000 to 5.0 million in 2015 (Zimmet, Alberti, et al., 2016). The burden of diabetes, including prevalence and number of adults with diabetes, has increased at a higher rate in low- and middle-income countries than in high-income countries (NCD Risk Factor Collaboration, 2016). Of the \$825 billion spent on diabetes in the world, 60% of the global costs are carried by low- and middle-income countries, where those with diabetes pay for much of their treatment out-of-pocket, leading to financial hardship. Health systems, especially in poor nations, are not equipped to meet the impact of diabetes on a global scale as the growing numbers lead to a heavy economic burden that impairs growth and development.

Of the estimated 451 million people who have diabetes, close to 80% live in low- and middle-income countries (IDF, 2017; Whiting, et al., 2011). In 2045, this number will jump to 693 million. The cases of undiagnosed diabetes are numbered at 212.4 million with 84.5% of all cases also coming from low- and middle-income countries. In 2017, 4.0 [3.2-5.0] million people aged between 20 and 79 years of age succumbed to diabetes, a number higher than the combined number of deaths from HIV/AIDS, tuberculosis, and malaria (1.1, 1.8, and 0.4 million respectively). Living with diabetes is difficult, with a great many carrying the burden of comorbidities and financial costs. While the countries and healthcare systems spend a great deal to cover the cost of diabetes, it is the individuals and their families who feel the economic impact most significantly. In the last ten years (2007-2017), the expenditure on diabetes has grown from USD 232 billion to USD 727 billion for those aged 20-79 years of age (IDF, 2017).

Type 2 diabetes is increasing in prevalence in most regions of the world (excepting European nations) because of economic development and resulting transitions in culture and lifestyle (Flávio Silva, Mendes Ferreira & de Pinho, 2017; NCD Risk Factor Collaboration, 2016; WHO, 2016). Changes associated with urbanization, globalization, and development has added to the burden of diabetes in all countries. There is a marked larger rise in prevalence in low-income and middle-income countries as compared to high-income English-speaking countries (NCD Risk Factor Collaboration, 2016). The rise in incidence is due to a group of factors; including increased adiposity (especially in women), genetic susceptibility from inadequate fetal and childhood nutrition in growth, poorly-resourced health systems and limited access to healthy foods and nutritional support (Crowshoe, et al., 2018; Leonard, Sorenson, Mosher, Spitsyn, & Comuzzie, 2009; Unnikrishnan, Pradeepa, Joshi, & Mohan, 2017).

As the prevalence of type 2 diabetes grows, direct and indirect costs also increase rapidly, especially in low- and middle-income countries. The growth of diabetes seriously affects many aspects of human existence, including society itself, global and national health systems, employers and diabetic patients and their families. Diabetes has a severe economic impact on those that suffer from the disorder and the medical system that takes care of them. This adverse effect increases with diabetes duration and the severity of the disease (Seuring, Archangelidi & Suhrcke, 2015). The cost of insulin and other medicines along with time lost from work due to illness burdens diabetic individuals and their families. The scarcity of resources for dealing with the associated clinical problems of diabetes in low- and middle-income countries leads to an unnecessary financial and health-related burden for those dealing with this chronic disease. In poor countries, the burden is carried by the individuals suffering

from the disease and their households due to limited healthcare coverage (Seuring, Archangelidi & Suhrcke, 2015). It is in these poor households where the burden of the disease is felt the heaviest. The poor carry no health coverage, so they must pay for medicine and health care directly from their own incomes, not from insurance policies. Economic adversity increases with how long a person suffers from the disease and how severe.

Countries and national health systems also carry a large economic load due to increased use of health services, loss of productivity and the extended support needed to treat diabetic complications (Cavan, et al., 2015). The globalization and marketing of industrial food products have caused many around the world to develop cardiovascular disease and diabetes at alarming rates. The term “nutrition transition” has been used to describe this trend in which nations, regions, and individuals undergo change and/or development that lead to problems in food availability, access, and cost (Leatherman, Hoke & Goodman, 2016). The nutrition transition usually follows a shift away from people consuming locally grown foods to commercialized imported highly-processed foods that can be bought in large quantities and at a low cost. These high-caloric foods that are rich in fats and sugars yet poor in nutrients lead to serious health problems related to overnutrition, especially type 2 diabetes. Beyond the severe effect on health, the shift away from locally produced foods is accompanied by an increase in the price of non-commercial foodstuffs, like produce, and the poor are faced with a loss in food diversity and food security. Lastly, environmental disturbances, including climate change and the contamination of food resources in global waters (i.e. PCBs, lead, mercury) has created serious obstacles in access to a high-quality diet and an increase in health problems, including

malnourishment and chronic diseases (cancer, heart disease, type 2 diabetes) (Blangy, et al., 2018; Gaudin, Receveur, Girard, & Potvin, 2015; Marushka, Sadik, Schwartz, & Ing, 2018).

1.1.2 Indigenous peoples and the burden of type 2 diabetes

“It does take self-control and willpower to eat healthily on a daily basis. But it is up to us to make ourselves physically and mentally strong again so that we may take care of our families and our Nations. We can only do so much to combat racism and prejudice, but we can control what we put in our mouths. We must take responsibility for our health and for the well-being of our children. In so doing, we pass on a legacy of self-respect and tribal strength to future generations.” (Miheshuah 2003, 828)

Indigenous people are the most vulnerable to food insecurity, malnutrition, and chronic diseases due to marginalization, poverty, discrimination, and environmental threats to their land and cultural resource that limits their access to healthy foods and leads to loss of identity and heritage (Gurney, Caniglia, Mix, & Baum, 2015; Kuhnlein, et al. 2013, 160; Tait, L'abbe, Smith, & Rosella, 2018). In 2014, the United Nations published a report titled *The State of the World's Indigenous Peoples: Health* to raise international awareness on Indigenous Peoples in general and to address the obstacles that impede their health. According to the report, Indigenous Peoples are the world's most marginalized. They live politically and socially isolated because of their geographical location, their distinct histories, traditions, and languages. Beyond isolation, Indigenous Peoples are often the poorest people in the countries where they reside. The poverty gap between Indigenous and non-Indigenous groups is growing in many nations in the world. These social determinants, including limited access to adequate health care, impede Indigenous People's fundamental human right to health and explain the rise of chronic diseases like type 2 diabetes within their communities. The chronic metabolic syndrome has reached crisis levels in Indigenous Peoples and the poor worldwide; with the highest rates

of type 2 diabetes reported in the Indigenous Peoples of Nauru, the United States, Canada, Australia and New Zealand (Koye, Magliano, et al. 2018).

Most of the world's Indigenous populations show a rapid increase in the prevalence of type 2 diabetes, markedly more than non-Indigenous populations (Yu and Zinman 2007). The shared experience of colonization and related displacement from their lands, the removal of access to resources, increased exposure to infectious disease and poverty, and the contemporary experience of racism and unequal distribution of the social determinants to health (income, employment, education, and housing) are all factors that can explain this increased prevalence (Crowshoe, et al., 2018; Oetzel, et al., 2017; Sittner, Greenfield and Walls, 2018). Yu and Zinham (2007) published a systematic review of the prevalence of type 2 diabetes (T2D) and impaired glucose tolerance (IGT) in Indigenous populations worldwide. They found that T2D and IGT prevalence rates varied widely between the different Peoples that they studied, noting a pattern of low to high rates within rural and urban populations of the same tribal affiliation, and the presence of a small number with a low prevalence rate.

Individual studies show that Indigenous communities are experiencing an increased rate of diabetes, acquisition at a younger age, and elevated cases of impaired glucose tolerance and pre-diabetes (Bream, et al., 2015; Espey, et al., 2014). Indigenous populations in New Zealand, Australia, the United States, and Canada have the highest rate of type 2 diabetes despite living in high-income countries with a well-established primary health care system that is mostly publicly funded (Gibson & Segal, 2015). Sadly, the healthcare and research communities in these wealthy nations have not served to improve the negative outcomes of type 2 diabetes while food insecurity and limited access to nutrient-rich traditional foods in

these communities further impede Indigenous patients with type 2 diabetes on their path to recovery.

1.2 Pathway to healing: decolonization of diabetes health model and treatment

1.2.1 Barriers to health and treatment in Indigenous communities of the U.S. and Canada

In North America, 565 Indigenous nations are federally recognized with each of these nations representing more than 500 tribal cultures, languages, traditional customs, and beliefs. (U.S. Department of Interior, 2010a, 2010b). In this diversity, Indigenous Peoples in North America share the health disparity of having the highest rate of type 2 diabetes when compared to all groups. There is a three-to-five-fold increase in the crude prevalence of diabetes among Indigenous communities when compared to the general population in the United States and Canada (Naqshbandi, et al., 2008). Those with diabetes also experience greater harm due to the co-morbidities that accompany the disease, acquire diabetes at a younger age, spend more during the course of their condition and have poorer treatment outcomes (Crowshoe, et al., 2018; Sanderson, et al., 2012).

Diabetes self-management is the single most important method in controlling and preventing the cascade of complications that accompany prolonged hyperglycemia. The conventional medical health model for managing diabetes focuses on lifestyle choices and a biomedical approach to treatment. This form of approach cultivates barriers to self-management for Indigenous patients because current programs do not consider cultural needs within tribal communities. Diabetes self-management education is centered around health care models that emphasize personal motivation, individualistic self-management plans and placing

the burden of care on the individual (Tiedt & Sloan, 2015). The Indigenous model to health is different, focusing on the reduction of stress and the return to a traditional way of living outside of colonialist pressures.

Individuals with diabetes deal with increased stress and physical challenges due to the comorbidities that accompany the disease, adversely affecting their quality of life. Their quality of life is improved when these individuals are supported by the tribal community and a health care system that provides culturally relevant health promotion education and a respect for cultural explanations of the disease unique to each tribal culture (Sanderson, et al., 2012, p. 59). In a study conducted by Sanderson et al. (2012), six elders from six different North American Indigenous communities were asked to share their perspective on diabetes, taking into consideration etiology, risk factors, increasing prevalence and co-morbidities. Any form of detachment from culture manifests in a departure from traditional subsistence activities and foods, the loss of language, stories, and physical separation from the land. The study addresses the role of elders in these communities who relate and preserve traditional ways of thinking during a time when separation from cultural roots is causing a loss of harmony and balance in physical, emotional and spiritual health, leading to chronic diseases like type 2 diabetes to take hold. The importance of the wisdom of traditional ways of knowing provided from elders in these communities and their act of sharing while the young adopt the traditional teachings protect against the encroachment of unhealthy lifestyles and acquiring diabetes.

Professor Waziyatawin, Indigenous Peoples Research Chair at the University of Victoria, is a Dakota writer, teacher, and activist whose research, writings, and speeches center on Indigenous decolonization strategies, including reparative justice, Indigenous women and

resistance, the recovery of Indigenous knowledge, and recovery and liberation in Indigenous communities. Her words resonate during a diabetes conference she attended:

“A group of us in attendance committed to the revitalization of our traditional ways discussed the importance of Dakota people re-turning to our traditional diet... we all agreed that in order to build healthy bodies, we need to return to a diet based on the plants and animals also Indigenous to our homeland. If we could sustain ourselves on the lean meats of venison, buffalo and fish, wild rice from our traditional lands, corn, beans and squash from our gardens, and the numerous berries, nuts and root vegetables we routinely harvested, diabetes would not be a health concern for future generations. The supposedly "superior" diet and food ways forcefully imposed on us have only served to deteriorate the health of our people.”

(Miheshuah, 2003, p. 828)

Prior to contact with Europeans, diabetes was not known among the Indigenous Peoples within what is now the United States and Canada. Non-native influences on food, the reduction in hunting, gathering, land-management practices and farming due to forced relocation and colonialist occupation led to the disease taking hold. A growing understanding of the role traditional, culturally-appropriate foods play in the health and well-being of Indigenous peoples has driven increased global interest in expanding the definition of food security. Food security is often described as resting on three pillars: availability, access, and utilization. Availability is having enough quantities of food on a consistent basis. Access includes the ability to purchase food or attain food from other sources and utilization is the ability to meet daily nutrient requirements (Walch, et al. 2017, p. 1).

Subsistence foods are essential to the well-being of the community. Physical health and cultural survival are threatened when the rate of food insecurity increases. In Canada, families in food-insecure households are more than two times at risk of developing type 2 diabetes than food-secure households (Tait, et al., 2018). In poorer households, limited budgets will compel families to purchase cheaper, high-calorie foods. These foods lead to excessive weight gain,

increasing the risk for the development of cardiovascular disease and type 2 diabetes. For the past two hundred years, federal policy disrupted agricultural and land management practices, forcing tribal communities off productive lands and altering nutrient-dense diets in the process. Beyond the stress of dislocation and disruption of cultural practices, these policies resulted in rising rates of food insecurity as they were forced into containment in reservations or moved to the city, where malnutrition reigned (Gurney, et al., 2015).

Difficult childhood events have been linked to health problems later in life. For Indigenous Peoples, stress is accumulative, and they are hit from multiple sides. Poverty compounds the stressors, and the capacity to manage diabetes is undermined. Mental health is crucial for any person suffering from a chronic disease, as the disease itself can cause a considerable amount of stress due to the discomfort of the complications combined with the need for disciplined self-care to manage the disease. Mental health disorders are prevalent in Indigenous populations who have undergone violence and oppression due to colonizing policies that have attempted to separate the People from ceremonial practices, access to land for food, technologies, and medicine, leading to a lack of local control of resources and a loss of cultural continuity (Valeggia & Snodgrass, 2015).

Another factor impeding the ability of Indigenous patients to practice healthy self-management of type 2 diabetes is nutritional health. The chronic nature of diabetes requires ongoing medical care and self-management to mediate blood glucose levels. The American Association of Diabetes Educators has outlined seven skills that assist diabetic patients with managing their disease: blood glucose testing, healthy eating, physical activity, taking medications, healthy coping, problem-solving, and reducing risks (Tomky, et al., 2008).

Traditional subsistence patterns have been interrupted due to the loss of access to lands that provide food along with dietary delocalization as traditional foods have been replaced by market foods of poor nutrition and quality (Noreen, et al., 2018). These losses have led to an unhealthy shift of diet from local, nutrient-rich and complex carbohydrate poor foods, to high-calorie, high-fat, high-salt, and low-fiber nutritionally poor foods (Kuhnlein, et al., 2013). Obesity combined with malnutrition are major issues in these cases as staple foods are available at a low cost. Malnutrition in the developing fetus and in children is related to obesity and related metabolic disorders in young female lives as they grow to adulthood (Leonard, et al., 2009).

Industrial pollution and the contamination of the rivers, lakes, and ocean is another factor in access to healthy food sources for Indigenous people who depend on fish, sea mammals, hard- and soft-shelled seafood, and sea plants, fungi, and seaweed for sustenance (Marushka, Sadik, Schwartz, & Ing, 2018). In Alaska and northern Canada, Indigenous Peoples have been warned by health officials to avoid traditional food protein sources due to environmental contaminants with toxic metals and chemicals, such as mercury, lead, and organochlorines (Gaudin, Receveur, Girard, & Potvin, 2015). Coupled with the loss of productive fishing due to plunging populations of culturally significant protein sources such as salmon and competition with commercial fisheries, environmental pollution has impacted not only access to traditional food resources but also the economic stability of First Nations of Alaska and coastal Western Canada and Washington state (Boxberger, 2007; Walch, Bersamin, Loring, Johnson, & Tholl, 2017).

Indigenous populations are faced with severe health service problems, including poor quality of service and inequities in treatment. Many providers ignore the social origins of disease when perceived from the Indigenous context of colonization and its exclusionary practices. Recurring themes of Indigenous experience of living with diabetes are language and communication barriers; appreciation of traditional food and lifestyle, and concern that the loss of these ways contributes to the development of diabetes; diabetes is a 'white people's' illness; and the identification of feelings associated with accepting diabetes (Bird, et al., 2009). The development of alternative strategies for treatment and prevention is necessary to overcome the threat of diabetes for the Indigenous Peoples of the world.

1.2.2 Cultural continuity and self-determination as protective agents

The colonization of North America required categorizing, dividing, and confining Indigenous people (Marker, 2009). The colonization of knowledge was a primary mechanism that colonialist governments would use to maintain power. Ethnobotanical and ethnoecological changes were brought on by the European and post-European occupations of land. Once the Europeans reached the Pacific Northwest, the lands and territories were appropriated by settlers who manipulated the land to serve their own purposes, turning resource-rich lands which had been managed for millennia by the Indigenous tribes into farmland and pastures for livestock. Colonial officials and religious leaders implemented laws that restricted Indigenous Peoples access to resources, religious freedoms, and ability to hunt and fish on their own lands. The settlement and colonization of the Pacific Northwest affected all areas of Indigenous life; food systems, technologies, medicines, ceremonies and belief systems, land management, fishing, and hunting systems. Coupled with the impact of foreign disease and weakened health

from malnutrition, the Indigenous population was reduced to genocidal proportions resulting in a great upheaval in social and cultural structures. Political and social systems were changed drastically as Indigenous social structures were manipulated by the banning of the potlatch ceremony, compulsory attendance at boarding schools, and an imposed economic system that revolved around wages.

An unseen result of colonialism and foreign occupation was the blocking of transmission of Indigenous knowledge between generations, resulting in the loss of connection to traditional food and medicinal systems (Turner N. J., 2014, pp. 192-193). Baptiste Ritchie, a Lil'wat elder from Mount Currie, told Dr. Nancy Turner in compiling the two-volume *Ancient Pathways, Ancestral Knowledge: Ethnobotany and Ecological Wisdom of Indigenous Peoples of Northwestern North America* about this occupation and loss of access to traditional food when he said;

“But now, because the white man really watches us, we don’t burn anything. We realize already. It seems the things that were eaten by our forefathers have disappeared from the places where they burned. It seems that almost everything has disappeared. Maybe it is because it’s weedy. All kinds of things grow and don’t burn. If you go to burn then you get in trouble because the white man wants to grow trees. Because they changed our ways they do good for us and we eat the food the white men use. Then we forget the good food of our earliest forefathers...We named other grounds of ours around here, called them ‘the Picking Places’ because that is where we went to pick berries. Now you will not find one single berry there.” (2014 ,p. 252).

Elise Krohn (2017) is a native foods specialist, herbalist, author and educator whose lifework is building relationships between plants, people, the land and cultural traditions. Krohn has developed native plant and food sovereignty educational resources and has coordinated community education programs that emphasize chronic disease and addiction prevention. Krohn has spent the last two decades teaching in tribal communities, working with elders and

cultural specialists to grow community gardens and enrich education with curricula on herbal medicine, native foods, and chronic disease prevention. In her work, she has been brightly inspired by the patients in the recovery programs she teaches. While her words reflect upon those who struggle with addiction and the power of cultural revitalization in their recovery, they can be equally considered powerful for those who struggle with managing diabetes:

“This is the moment I hope for as an educator. The patients are remembering who they are and where they come from. They are beginning to recover their own wealth, and therefore to heal themselves and each other. Not only is this one of the greatest tools for recovery, but it is what the patients carry home from these events and their recovery spreads to others. Patients must be able to see themselves in their recovery. Their culture is their medicine. Native plants, singing, drumming, a sweat lodge, beading, and support from local native spiritual communities are part of the program. These act like pillars to hold patients up during their recovery. When patients’ traditions are honored in the healing process, retraumatization is less likely to occur.” (2013, pp. 93-94)

Cultural continuity (the preservation of traditional culture in the present) and the strength of community bonds heals many wounds. Oster et al. (2018) conducted a study in which the team used a mixed-methods approach to relate how cultural continuity and self-determination affects the prevalence of type 2 diabetes among the Cree and Blackfoot Nations of Alberta, Canada. The following quote is taken from the study and refers to a holistic concept of culture beyond that defined by academia:

Culture contains all of the teachings and direction on “how to walk in this world” and includes, but is not limited to, traditions, values, knowledge, hunting and trapping, living off the land, traditional food, medicines, games, sweats, spirituality, ceremonies, celebrations, praying, and language. Participants viewed having culture permeate all aspects of life as “an Indigenous way to live” and “a harmonious way to live”. (Oster, Grier, Lightening, Mayan, & Toth, 2014, p. 1)

In the study, Oster et. al interviewed Cree and Blackfoot council officials asking them to discuss what ‘cultural continuity’ and ‘self-determination’ meant to them and if and/or how these

concepts related to health and diabetes. A major finding from the interviews with council leaders was that a strong attachment to culture (as defined previously) was the most relevant factor in health and recovery from diabetes. Participants in the study also emphasized the close relationship between language and culture such that the two co-exist as one entity with language being at the center of culture itself. The link between traditional knowledge and health was another concept celebrated in these interviews with participants saying:

Our traditional knowledge services have been such a shining light in the darkness because it's so promising, and people are starting to have a lot of respect for it and wanting to be a part of it. The values generated out of that will take care of people, whom will take care of each other. The compassion, the generosity, those are our traditional values. When we remain a collective society, and when that's our value system, that takes a lot of work and (leads to) ethics in leadership, respectful relationships, spirituality and healthy relationships. (p. 4)

Another study conducted by Shaw et. al (2012) addressed the psychosocial needs and perceived barriers to management of diabetes of 13 AI/AI adults receiving treatment at the Alaska Native Primary Care Center (Anchorage) using three key themes: resources for managing diabetes, roadblocks to managing diabetes, and turning points in the trajectory of the illness. Knowledge and education about diabetes, social support, spirituality, and self-efficacy were the most common resources revealed in participant narratives. According to the participants, the roadblocks to treatment were lack of knowledge about personal nutrition and diet, social difficulties caused by dietary restrictions and comorbid medical problems caused by complications of diabetes itself. Participants found that these 'roadblocks' were removed when they were empowered by their ability to manage the disease with dietary changes and healthy choices in physical and emotional activities. While the study addressed the overarching themes in effective self-management of the disease for the Indigenous participants, the social scientists

neglected to address the role of cultural continuity and cultural resources in the participants' lives. Nonetheless, the findings from the study point to the need of culturally-appropriate education programs for Indigenous patients who may find victory in their internal battle against managing the disease with the help of knowledge, social support, spirituality, and personal transformation.

Many current health programs fail to improve the health of Indigenous communities due to ignorance of the cultural, spiritual, and physical needs of diabetic patients. Medical practitioners that focus on a holistic approach using restorative programs that work to treat the whole person, restoring spiritual, emotional, physical, and material wellness understand the appropriate course of treatment for Indigenous patients with type 2 diabetes (Smith L. T., 2014). Those programs that seek to connect with the community using restorative models based on healing intergenerational trauma and focusing on positive health through reconnection to the traditional foods, language, and family result in healthier clients.

As the disease takes hold in these nations due to the prevalence of poverty, malnutrition in the guise of obesity, and inadequate access to medical resources; there is a comfort in knowing there are medicinal plants found in the local environment that offer treatment for the disease. The Coast Salish of the Pacific Northwest have a substantial repertory of healing foods, plants, and traditions that have been tested through Indigenous scientific methods and biomedical science to support health and prevent disease, specifically, type 2 diabetes (Körn & Ryser, 2009). In western Canada, many people prefer an alternative, traditional healing system for the treatment of various ailments, or for the maintenance of health. Health care administrators and practitioners who honor the role of traditional medicine

and include Indigenous healing science with “western” scientific healing methods will have more success in treatment outcomes in diabetic patients (Turner & Hebda, 1990, p. 71).

Continuity of culture is identified as a protective agent against destructive behaviors, like drug and alcohol addiction, and non-communicable diseases, like diabetes, in Indigenous communities. Indigenous healing systems are holistic in scope, involving spirituality and a close connection with the natural environment where the whole community is involved in the healing process with local experts who are consulted to provide knowledge that aids the sick (Uprety, et al., 2012). Diabetes prevalence found to be lower among remote Indigenous populations is correlated with cultural continuity, the contemporary preservation of traditional Indigenous culture and language, and the revitalization of traditional foods (Oster, et al., 2014). I conclude with the words of Edgar Ninguelook (Inupiat) of Shishmaref, Alaska, a small island in the Arctic currently undergoing a crisis as their island is slowly falling into the Arctic due to erosion caused by melting ice;

“We are the only ones who can save ourselves. We keep looking at the outside world for someone to come and do it, and it’s not going to happen. We are expecting someone out there to save us and, in fact, there is nothing in the outside world that is really that important...I think our people ought to understand that it is possible to maintain their identity and their spirit, their language, their traditions, and history and their values and still function in the twenty-first century. We know what we need to know, how to make decisions, how to analyze situations, how to speak many languages and understand technology.”
Edgar Ninguelook Shishmaref, Alaska (Mather 1995, pp. 24-25).

Chapter 2 *Oplopanax horridus*

Before the European explorers and settlers occupied the lands of the Pacific Northwest, the Indigenous Peoples had developed a diverse collection of oral traditions that delineated personal and tribal histories along with establishing continuity in myth regarding animal and plant beings. Oral traditions give a beautiful picture of the history and culture of these Nations using narrative based in spoken word, offering a form of understanding not limited by written forms. Indigenous oral narratives give a wealth of knowledge, including the use of plants as medicine and in ceremonial rituals. This chapter begins with defining oral traditions, oral myths, and oral histories and is followed by a specific discussion about the role of plants in these traditions. The core of this section is devoted to presenting to the reader written translations of narratives gathered by Franz Boas, George Hunt, and Henry Tate. These stories are specific to the plant devil's-club and offer depth in the description of *Oplopanax horridus* and its intimate relationship to Pacific Northwest Indigenous Peoples. The middle section of the chapter is a description of the physical characteristics of devil's-club, including botanical description and range. The ethnobotany of *Oplopanax horridus*, especially with regards to medicinal uses in individual Nations, is also included to give an overview of the plants vast medicinal capacity. I conclude the chapter with an explanation of the chemical and pharmacological components of the plant to provide the necessary chemical background that built my impetus to research the root bark in the lab.

2.1 Oral traditions and devil's-club

“Stories are not merely narratives to fill time or to lull a child to sleep; they are vehicles of cultural transmission that allow spiritual knowledge transfer. . . along with the emotional (feelings conveyed by the story's narrative), physical (sound vibrations), and intellectual (a traditional teaching).” (Marshall, Marshall, & Bartlett, 2015, p. 22)

2.1.1 Oral myths, oral traditions, and oral histories

The definitions of ‘oral myths,’ ‘oral tradition,’ and ‘oral history’ have shifted in meaning through the course of time. Some oral historians have described these traditions, usually identified as myths or stories, as a way that cultural items (or data) are transmitted from one generation to the next (Showren, 2014). According to Julie Cruikshank (1994), Professor Emerita of the University of British Columbia, the term oral tradition can refer to a body of material of the past or a process through which information is transmitted from one generation to the next. Cruikshank defines oral history as a research method in which a sound recording is made of an interview about the first-hand experience lived through the words of an eyewitness. An oral myth has been defined as events that occurred during the time of animal people, events which established the plants, animals, geography, even behavior patterns for the time of human people (Thompson, 2011, p. 20). Oral traditions, including myths, narratives, and histories, represent complex cultural patterns that continue to hold power and meaning for contemporary members of Indigenous communities and are here to forth respected as the property of those who told them (Thom, 2003: p. 21).

Oral traditions carry many roles, being testimonies, legal documents, sacred documents, and a source of medical knowledge. They are narratives and narratives do not move in a straight line in time nor is it simply a linear chronology of the past. Rather, these stories and

myths exist in a timeless universe, living to breathe threads of connectivity between the past, present, and future. Oral myths penetrate time and space, inseparable from the culture and language that carry this tradition. Levi-Strauss eloquently described the quantum ability of a myth to defy time when he wrote:

On the one hand, a myth always refers to events alleged to have taken place in time: before the world was created, or during its first stages-anyway, long ago. But what gives the myth an operative value is that the specific pattern described is everlasting; it explains the present and the past as well as the future (1955, p. 430).

Oral traditions and myths are cultural testimonies that describe events specific to a time and a place, or events that occur through time and space, and should not be taken out of this culturally mediated context (Cruikshank, 1994, p. 409). Anthropologists, I included, may take these testimonies and attach a meaning that moves the true meaning of the text away from its cultural and historical context; creating a gap of meaning between the original narrator and that defined by the anthropologist (Thom, 2003, p. 3).

Elsie Mather (1995), a bilingual educator, nurse, interpreter, language specialist, writer and member of the Yupiit of Southwest Alaska, has worked on the preservation of Yup'ik traditional stories by writing down narratives that had been carefully passed by elder storytellers in her community. Part of Mather's life work is the preservation of values and customs from oral literature for future generations in her community, so they grow to have a sense of responsibility and respect as taught by their ancestors and elders. In her 1986 address to the Alaska Bilingual Multicultural Education Conference "With a Vision beyond Our Immediate Needs: Oral Traditions in an Age of Literacy," Mather speaks of what her elders indirectly taught her through the stories they told:

“It is not their story. It was passed on to them. They claim no authority about what they tell you. More importantly, they are telling you what a great responsibility it is to be able to learn from others, to cherish that knowledge, and then to pass it on carefully. They seem to feel the enormity of this situation, and often they have no way to pass on their sense of responsibility and their knowledge to the rest of the people. We, as materials developers, writers about our cultures, should feel that same respect for the information we receive from our elders. Like them, we ought to make it clear that some knowledge is not our own but that we are passing something on that we acquired from a respected source. Our traditions are very important to us. They carry something immortal, and to make them sound as if they are coming from us is an insult to our culture and our elders, who themselves make it very clear that they are only vehicles.” (1995, p. 17)

Ancient narratives of the Indigenous Peoples of the Pacific Northwest are, as all Indigenous oral traditions, the intellectual property of the individuals and their lineages who spoke them into being and it is important to remember that these stories were told in their own Indigenous languages (Wehi, Whaanga, & Roa, 2009). The narratives provide for the People a sense of place and belonging, speaking into being plants and animals, birds, fish, rivers, and mountains as active members of the environment, united together in time and space, with no separate layers dividing them (Turner, 2014, p. 233). The published texts and translations that are referenced in this work have been translated from the Indigenous language, and in the case of those from Boas, are the result of two or three translations. Further, these stories must be remembered in their historical and cultural context, in which moral and social messages are a part of a larger context in terms of society, history, and politics.

2.1.2 Oral testimonies: a source for medicinal knowledge and ceremonial significance

“We argue that oral traditions offer a wealth of information that is frequently overlooked, in part because of a lack of knowledge of *te reo Māori* (the Māori language) and further a lack of recognition of the inextricable link between biological and cultural diversity.” (Wehi, Whaanga, & Roa, 2009, p. 201).

Oral tradition serves not just to preserve history. Detailed knowledge of plants, including the identification, habitat, seasonal variations, and medicinal applications, is embedded in the narratives, reflecting an integrated system of knowledge (Lynne, 2015). Indigenous oral traditions are a valuable source of information for researchers, yet they are not discrete units of historical fact that should be used merely to legitimize scientific data. These testimonies are also cultural documents that organize perceptions about the past and should be conceived as an entire text to be read in the context of social organizations, the language and culture from which it was spoken, the gestures and dialogue inherent in its presentation; not pieces of information to be interpreted by the outsider (Rosaldo, 1980; Showren, 2014). In this work, oral traditions, oral narratives, and myths will be used interchangeably and will be considered, yes, as cultural documents; but, more importantly, will be contemplated in the light of Nuu-chah-nulth hereditary chief and scholar Dr. E. Richard Atleo's (Umeek) words:

“...these stories are *true*. They reflect different *dimensions* of truth, serving as parables and ways of remembering the past, encoding memories, lessons, and approaches, and passing them on to future generations in an effective and meaningful manner. Storytelling is about conveying truths at a metalevel and is therefore highly important as a means of transmitting critically important ideas and information in a given cultural context.” (Turner N. J., 2014, p. 232)

Indigenous narratives focus on the intimate relationship between place, people, and plants, where plants on the landscape link social structure and presence on the land (Johnson 2013, p. 89). Storing, maintaining, and transmitting a large body of scientific and cultural knowledge is valued in these oral traditions (Lynne, 2015). Animals and plants are often present in the songs, stories, mythology, and art of past and present oral cultures, serving as food, shelter, clothing, relatives, and spiritual beings (Lynne, 2015). In the ancient times that are described in these stories, the spiritual beings interacted directly with humans, and there did

not exist a separation between the spiritual and physical world. Mountains, rivers, trees, plants, and animals existed and were named as human persons through which humans and spiritual beings moved between many different worlds. Plants play different roles in these narratives, appearing as supernatural entities, medicinal references, technological parts, and are identified in these texts as food, materials, and medicine, revealing a profound cultural significance. The knowledge of medicinal plants has been passed from generation to generation through these narratives.

What is the role of myth in studying disease treatment and remedies found in plants mentioned in these texts? The oral testimonies presented here are more than a list of medicinal uses and preparation of devil's-club. They speak of the value of this plant, its revered place, and describe ceremonies that are honored spiritual traditions. Devil's-club is mentioned several times in these records of oral myths, validating the presence of this plant as a powerful symbol of medicine and its sacred status. These myths and stories reveal a deep-rooted living knowledge that regards the medicinal and spiritual value of devil's-club. These verbal texts are rooted in the culture for hundreds of years. Numerous sources, including Boas, Garfield, Gunther, Smith, Turner, and tribal publications write of the multitude of uses of devil's-club, spanning from ingesting the inner root extract to treat tuberculosis to ceremonial imbibement to elicit protection from spiritual adversaries.

2.1.3 Oral traditions and devil's-club: Boas' fever to acquire knowledge

"In these two sentences, we probably have as pregnant an expression of Boas' objectives in the field of cultural anthropology as he will permit himself. Professor Boas would be the first to object to generalizations on the basis of his subjective statements, yet I feel that we have epitomized here the threefold purpose of his insistence upon careful comparative analyses. First, they may reveal certain historical trends; secondly, they

may yield those features common to region or even to mankind in general, and lastly, they give the truest appreciation for the uniqueness of each tribal configuration.” (Du Bois, 1937, p. 143)

Anthropologists and ethnographers have recorded a selection of Coast Salish oral stories passed down from generation to generation. These stories speak of the medicinal and spiritual value of devil’s-club (Boas & Tate, 1916; Boas, 1923; Boas, 1930; Krause, 1956). The earliest fieldwork at the hands of Franz Boas, William Beynon, Henry Tate, and Marius Barbeau involved the transcription of oral myths and religious traditions in a text form. In these records, explicit details of certain ceremonies with the root bark of devil’s-club are explained, revealing medicinal and spiritual treatment methods. Franz Boas specifically collected and published into written text the Northwest Coast oral traditions more than any other scholar to the present time. Boas viewed these texts as sources of data that explained the history and culture of a People he was studying. From the position of cultural relativism, Boas documented these oral traditions in hopes that the words transcribed would offer an authentic representation of what was important to the People in their own words, as opposed to an ethnography written from the perspective of an outsider (Du Bois, 1937; Thom, 2003). Boas intended to present these texts from the perspective of the narrators themselves to paint “a picture of their way of thinking and feeling free from the bias of the European observer as is possible” (Boas, 1935: v).

Boas hired Indigenous-speaking scholars to transcribe the oral traditions in the language from which they were spoken, hoping to describe a culture from the inside or emic perspective. Indigenous scholars George Hunt, William Beynon, and Henry Tate interpreted the oral histories to written English. Beynon and Tate collected and translated oral tradition from the keepers of oral history and knowledge among the Tsimshian of British Columbia. Boas used these texts to

base his ethnographies on the Tsimshian and Kwakiutl Peoples, interpreting the myths to draw out cultural data regarding their social organization, customs, arts, and material culture. These texts describe myths separated into different cultural items: family and tribal organization, ethics, ceremonial objects and practices, material culture, personal and family life, supernatural power, beings and objects, animals and plants, and the origin of family-owned and sacred geographic places and features. A major critique of these collections is that Boas made broad assumptions regarding a culture using traditions transcribed from a specific tribe. Another critique of Boas' methodology of describing local customs or beliefs using the translated texts is that these represent a one-sided view as told by the storyteller and received by the transcriber and translator and may contain borrowed events that represent cultural practices that are not local (Barbeau, 1917).

Franz Boas created two major collections, the Tsimshian and Kwakiutl texts, while living in the communities in which he was documenting. George Hunt (Tlingit), and Henry Tate (Tsimshian) collaborated with Boas on these language and ethnographic projects, creating a what Boas believed to be a thorough collection. Boas collected hundreds of pages of Kwak'wala texts on his own. Hunt phonetically transcribed the Kwakiutl texts and then translated them into English and sent the transcriptions and translations to Boas in New York to be reviewed, corrected, and later published. The collection of Tsimshian texts was recorded by Henry W. Tate of Port Simpson, British Columbia, in Tsimshian, Tate's native language. Boas used literal interlinear translations to translate Tate's Tsimshian texts into English. In the translated texts by Boas and Tate, the myths describe a time in which supernatural beings walked on the land with

humans, moving through different worlds and used their powers to shape and build the world of the present time.

Tsimshian oral traditions are called *adawx*, a complex body of texts that were inherited as heirlooms within lineages and relate to significant events in the history of families, lineages, clans and village groups (Martindale, 2006). Each Tsimshian lineage owns its own *adawx*, texts that legitimize the lineage's place in the social and geographical landscape (Martindale and Marsden, 2003). Martindale considers the *adawx* as both narratives of the past and textual artifacts of the present. In Tsimshian society, oral traditions play a sacred role connecting ancestors to descendants and people to the landscape while invoking both a secular history along with a spiritual history to instruct present generations (Martindale, 2006). It is important to recognize that local myths and histories were the personal property of houses, clans and chiefs, an exclusive privilege specific to those who held the stories (Barbeau, 1917). In reference to this ownership, Tate collected myths and stories that were purely public domain, not individually owned by lineages or families.

Boas and Hunt worked together for forty years to purchase artifacts, to photograph and record, absconded skeletal remains, and sold sacred objects to be shown in museum collections. Boas made charts showing how vowel sounds were articulated using the system of phonetic transcription. George Hunt's father was an English fur trader who married Ansnaq (Taantakwáan) of the Raven phratry, the Tlingit daughter of Chief Tongass from the southern Alaska Coast. Ansnaq, or Mary Ebbetts, and her husband moved to Fort Rupert on Vancouver Island where they ran an outpost and a Hudson's Bay Company station. George Hunt, Maxwalagalis, Q'ixitasu', was born on February 14, 1854, and grew up among the

Kwakwaka'wakw, learning the Wakashan language, Kwak'wala. Being the son of a noblewoman, Hunt understood the knowledge and discourse of elite lineages, especially after he married a high ranking Kwakwaka'wakw woman. Hunt worked for Boas for 45 years as an informant and a translator of the Kwak'wala language for numerous texts, including the Kwakiutl texts and the Religion of the Kwakiutl. Hunt also acquired a vast amount of material culture for white collectors and is responsible for obtaining the majority of items for the World's Columbian Exposition in Chicago (the Field Museum), the American Museum of Natural History, and the Museum of the American Indian (Briggs & Bauman, 1999).

The following narrative from Boas' (1930) The Religion of the Kwakiutl is transcribed and translated by George Hunt. The account begins with a woman in great pain who sends her husband away to gather devil's-club. Before he cuts down the plant, he prays. Then he chops down four stalks of the devil's-club, wraps them, and takes them home where he scorches off the thorns and peels off the bark. The piles of bark are placed in a kettle and boiled for hours under water. The husband prepares a steam bath for his wife using the devil's-club tea. The ailing woman lays on the planks for such a time that she sweats, drenches her clothes and is relieved of her pain. The narrative concludes with a prayer that pleases the Supernatural One to take away the pain when using the powerful combination of devil's-club tea and seeds from the wild carrot family.

Devil's Club

And that, when a woman, or a man, has pains in her body, then the woman who has been in bed for a long time with pains in her body sends her husband to go to a river where devil's club is growing to get a devil's club plant. At once the man takes his small axe and an old mat and he

goes out of his house. He walks up the river and when he arrives at a patch of devil's club plants he sits down and, looking at the devil's club plants, he prays and says,

"Now look at me, for I come trying to come to you, great Supernatural Ones, being sent by my poor wife and I come and ask you for mercy that you, please, take out her sickness; that is the reason that she had been lying in bed for a long time sick with pains in her body. Now I come to call you, Supernatural Ones, that you may go, please and save her, you, Life-Giver; and you also, Healing-Woman, that you, please, may set right my poor wife, please, that you wash off her sickness with your water of life, that, please, she may live, please," says he as he stands up and takes his small axe and chops down the devil's club bush.

As soon as he has chopped down four he chops off the tops and after he has done so he takes the old mat and spreads it out on the ground. Then leaves the four pieces of devil's club down on it. He wraps the old mat around them and he takes them on his shoulder as he goes home. As soon as he enters his house he puts down the old mat containing the devil's club and puts it down by the side of the fire. Then he builds up the fire and as soon as he has built up the man takes the tongs and with them picks up one piece of devil's club and puts it on the fire so that all the spikes are scorched off. As soon as they are scorched off he puts it down. He does the same with all the others.

As soon as he has done so he takes his knife and a small mat and he spreads it on the floor at the place where he is sitting where the devil's club is. Then he takes one piece of devil's club and peels off the bark and puts it on the small mat. When all the four pieces of devil's club are peeled he takes a kettle and puts the bark of the devil's club into it. When it is all in he pours water on until the kettle is full of water. Then he puts it on the fire. Now the whole day long it is boiling. When it is evening, he takes it off the fire, then the man takes a tub and he puts it down where his wife is lying down sick. He takes the tongs and with them he takes out the bark of devil's club and puts it down on the floor. As soon as it is all out he takes up the kettle and pours the juice of the devil's club into the tub. Then the man takes a short board and puts it across the tub.

Then the woman goes to sit on the board. Her husband takes two blankets and puts the mover his wife. The edges hang down around the tub, for he does not want the steam to go through. For a long time the woman is sitting there. Then the woman perspires on her face, for it is very hot. When the woman cannot stand the heat she stands up and goes to her place where she lies down. Then / she takes off her wet shirt and she changes it for a dry shirt. Generally, the pains in the body of the woman get well when she does this, steaming with the devil's club juice, for that is the name of the medicine. Sometimes they put a handful of Peucedanum seeds into the devil's

club steam bath, for this is a very strong medicine. This is the prayer of the woman when there are the two kinds, devil's club / and Peucedanum seeds. She says,

"You have come, great good Supernatural One, and, please, help each other with your powers that you, please, make me well, for I am poor. Go on, please, take out this cruel sickness, you, Healing Woman, you, Long-Life-Maker, please," says she. That is the end. (Boas 1930, p. 242)

This narrative describes the preparation of the bark of devil's-club to treat pain and refers to the plant directly as strong medicine. Yet, this oral transcription is more than a flat description of a specific plant medicine. The prayers to "the Supernatural One" Healing Woman and Long-Life-Maker bring a spiritual depth and relationship between the plant, the woman and her husband, and the "Supernatural Ones." These interrelationships are distinct from the approach used by conventional medical and Western scientific paradigms of research in plant medicine. This holistic manner in medicine and recognition of a spiritual connection between nature and Indigenous People represents an Indigenous research methodology that protects cultural continuity and Indigenous ownership of the medical knowledge.

Oral historian William Beynon (1888-1858) was a Nisga'a hereditary chief of the wolf (laxgibu) phrarty from the Nass River village Gitlaxt'aamiks. Beynon married the niece of the chief of Kitkatla and became a prominent member of the Coast Tsimshian society due to his chiefly lineage and marriage to a high-ranking woman. Beynon was hired by Marius Barbeau as a field laborer, assistant, and translator during Barbeau's first field season on the north coast. Beynon was paid \$25.00 for each notebook he filled, with each book containing one hundred pages. During the first season, he lost most of his fee in a shipwreck and paid out of his pocket to his Indigenous informants. Beynon worked for Barbeau for thirty years, supplying the French-Canadian anthropologist with 3,000 handwritten pages in which he recorded maps, house lists,

myths, rituals, raid, accounts of feasts and secret ceremonies, and narratives primarily from the Tsimshian village of Kitkatla (Winter, 1984). The following narrative is taken out of the Tsimshian Recordings; it is a partial transcription of the origin story of devil's club as told by P. Ryan to William Beynon.

The Origin of Devil's Club

The people who had deserted the young woman and grand-mother now returned to their village of Metlakatla and the chief wondered what happened to his relatives they had deserted, so he said to the tribesmen, "Go to the nearby camp at K'met-Ku and if anything can be found of their remains cremate them. They must have perished from starvation." So the tribesmen set off and behold when they came to camp, they saw a large house and they landed below this and going up they found the young woman and her grandmother both very busy preparing food. They saw that the house was filled with foods of many kinds and were somewhat embarrassed and the young woman said. "You have come from my uncle and since we have come here, we have learned much since we have come here. Many things that will benefit not only my uncle, but all his people, so that they shall become the most prosperous people on earth." Food was given to her uncle's tribesmen and some to take back with them for her uncle. When they returned the spokesman said, "We were astounded at the wealth of the young woman and her grandmother they have a large house which is full of all different kinds of food, sea and mountain foods, and all kinds of strange bark. Your niece and her grandmother told us that they have something which will make us the most powerful people of all the other tribes. She told us no more, so we advise you that you should go and fetch them here to your house."

The chief at first feeling embarrassed, finally he called together his people and said, "We will go at once and bring them here." They set out with his tribe and landing where the young woman and her grandmother were living and then the chief said to the women, "I have now come with my tribe, to fetch you to your own house and we take all your belongings." They then packed all that was in the large house into many canoes and then set off their village at Metlakatla.

When they had settled into the house of the great chief, the young woman, they gave a feast to which the uncle's whole tribe were invited into the house and then the young woman spoke to them. "While we were at 'Kmetku, a supernatural being visited and helped us and he had been sent by his father who was the chief of the 'wa'ums. He first gave us plenty of food and then built the large house that you see. Then he also showed us the 'wa'ums plant and all its uses and

powers and how to prepare it and what its powers are to be used for. For purification purpose it must be used in such a way and respect, so that its powers will not flare back on the one using it. It will purify a hunter so that the animals are unable to smell the human scents, smelling only the 'wa'ums scent. Also this 'wa'ums is to be used in times of sickness for many ills. All of these things the supernatural being has shown me and I will now teach you all the showed me, then we in turn can do this to all the other Tsimshian tribes and in doing so we can lead them all." So the young woman taught all of her people the uses of the 'wa'ums. Also she showed them the method of purifications and that during this period that they must keep away from contact sexually with each other. In a short time the people began to know of its use of the 'wa'ums and its powers and soon their hunters were very successful and the tribe now always had plenteous supplies of food and other wealth, so now they began to be called upon by the other tribes to teach them the uses of this 'wa'ums. This is the story of the origin of the 'wa'ums. (Devil's Club) (Ryan, 1952, pp. 46-47)

2.1.4 Shaman and sacred plant use

"If a person wants to become a shaman he goes and "counts days." He purifies himself by washing and must be continent. He rubs his body with devil's club (? wēq!as) and he drinks a concoction of the plant. He washes with blue hellebore and drinks a concoction. He rubs his body with juniper (d'ēsīdemala's)." (Boas, Bella Bella (Heiltsuk) notes, 1923, p. 268)

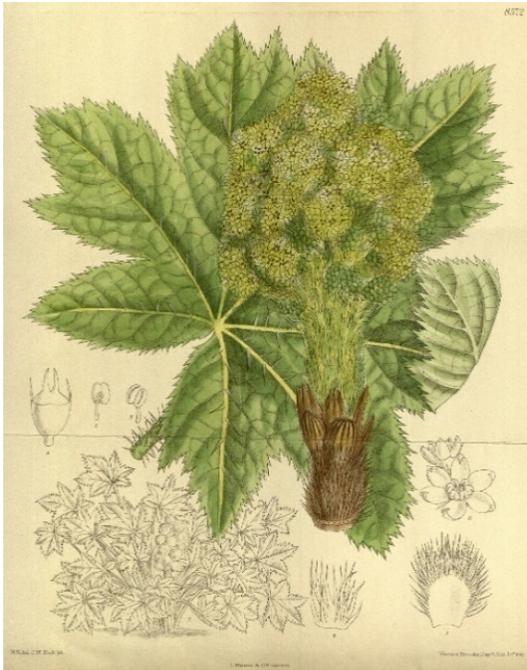
In northwestern America, historical Indigenous healing systems are focused within two distinguished areas of healing and medicinal practices, shamanism and herbal medicine (Turner, 2014, p. 440). When illness occurs, the first approach is through herbal medical treatment. When herbal medicine did not heal the illness, the sick would seek the healing ways of the shaman who would use plants in a spiritual way through a ritual to ascertain the source of illness or gain healing powers over the illness. Shamans were subjected to years of rigorous training which involved long periods of isolation, fasting, and ceremonial cleansing to prepare them for their practice of medicine as well as their role as spiritual leaders (Turner, 2014).

Shamans would often cleanse themselves internally with plants that have emetic or purgative effects, such as devil's-club. For example, the Tlingit shamans would chew the roots

of devil's-club and swallow the juice to augment "hypnotic" powers (Gorman, 1896). Devil's-club use by shamans is mentioned in several stories as a protective agent against evil and to acquire supernatural help. Evil is indicative of pernicious behavior, one that causes harm and is morally reprehensible. The diseases that were brought to the Pacific Northwest were evil, they took the lives of thousands, decimated populations, and weakened the economic ability of community members to acquire wealth in the form of resources and food. Symbolically, the protection from disease is a primary attribute of the plant. The nature of Indigenous medicine is holistic; the supernatural is not separated from the physical, and the land is not separated from the people. The long-time usage of the decoction of devil's-club as medicine and to enhance the shaman's spiritual experience carry through to this day in which active constituents within the plant continue to protect Indigenous communities from contemporary diseases that threaten their health.

2.2 Physical characteristics and range of *Oplopanax horridus*

Oplopanax horridus



Rank	Scientific Name and Common Name
Kingdom	Plantae – Plants
Subkingdom	Tracheobionta – Vascular plants
Superdivision	Spermatophyta – Seed plants
Division	Magnoliophyta – Flowering plants
Class	Magnoliopsida – Dicotyledons
Subclass	Rosidae
Order	Apiales
Family	Araliaceae – Ginseng family
Genus	<i>Oplopanax</i> (Torr. & A. Gray) Miq. – oplopanax

Figure 1: Devil's-club (*Oplopanax horridus* (Sm.) Torr. & A. Gray ex. Miq.) by M.S. del., J.N. Fitch lith. [Public domain]

Man-high ferns and even taller huckleberry and rhododendron are associated with the peculiar west coast Araliacea (Fatsia horrida Smith.), called devil's walking stick by the Americans, whose slender stem is surrounded by a circle of large, hand-shaped leaves which, like the stems, have countless fine spines that with careless handling penetrate the skin and cause unpleasant soreness. Aurel Krause geographer (1956, p. 57)

Devil's-club (*Oplopanax horridus* (Sm.) Torr. & A. Gray ex. Miq., Araliaceae) is an erect and sprawling deciduous shrub (1-3m) with long, thick, ascending stems and large, palmate-lobed leaves. **Figure 1** The large maple-like leaves measure up to .4m and have wide-irregularly shaped serrated margins and long petioles, or stems (Hitchcock, et al., 1961; Small & Catling, 1999). The petioles, leaves, and stems are densely armed with sharp, thin spines 5-10mm in length. These spines break off easily on contact and are difficult to remove subdermally. Once

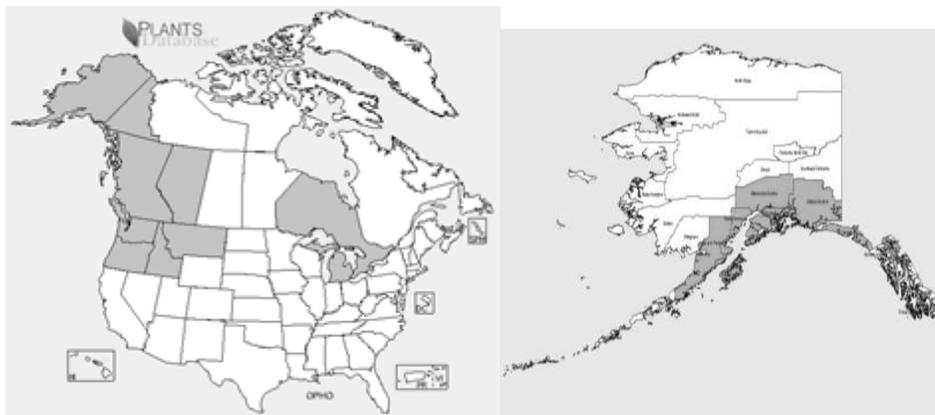
imbedded, the thorns are extremely irritating and may fester in the skin (Krause, 1956). Devil's-club blooms from May to July with small (5mm) greenish-white flowers that are tightly bunched together atop short stalks arising from the main stem of the inflorescence in a formation known as a panicle (Howard, 1993; Kozloff, 1976). These flowers later develop into little fruits as bright, red berries with a flattened ellipsoid shape in pyramidal terminal clusters (Haskin, 1967; Pojar and MacKinnon, 1994). Even the berries are sometimes spiny.

The genus of *Oplopanax* (Torr, & A. Gray) is part of the ancient angiosperm plant family Araliaceae and consists of only three species: *Oplopanax horridus* (Sm,) Miq., *Oplopanax japonicus* Nakai, and *Oplopanax elatus* (Nakai) Nakai (Shikov 2014). All three in this genus share the attribute of being used medicinally in their region of origin. *Oplopanax japonicus* (Nakai) grows in the northern mountains of central Japan. The shrub, known in Japanese as *Haribuki*, is used as a local remedy for a cough (Takeda, Minato, & Ishikawa, 1966). *Oplopanax elatus* grows in mixed forests (1400-1600m) throughout temperate regions of Northern China, Korea and Russia (Shu, 2007). In Chinese medicine, *O. elatus* (Nakai) has been used to treat cardiovascular disease, rheumatism, schizophrenia, and diabetes mellitus (Shikov, 2014). The stem of *O. elatus* is reported in traditional medicine and scientific literature to act as an analgesic to treat arthritis and exhibits antimicrobial activity (Calway, et al., 2012).

Oplopanax horridus is distributed from coastal Alaska southward, on the west side of the Cascades to southern Oregon, eastward to the Rocky Mountains (including parts of Idaho, Montana, and Alberta) and in a small population near northern Lake Superior (Howard, 1993).

Figure 2. *O. horridus* grows amidst the diverse flora of Pacific Northwest; being found growing with other shrubs like Alaska blueberry, red elderberry and red huckleberry in the understory of

grand forests that contain western red cedar, western hemlock, red alder, Sitka spruce, and amabilis fir. This impermeable shrub prefers to grow in the understories of mature to old-growth forests on moist to wet, rich soils near stream edges, on floodplains and in seepage sites (Kozloff, 1976). Devil's-club growth and expansion persist through all stages of forest stand development, ranging from high light intensity in clear-cuts to low light intensity in second- to mature-old growth forests (Lantz & Antos, 2002).



Source: <https://plants.usda.gov/core/profile?symbol=OPHO>

Figure 2: Range map of *Oplopanax horridus* regions shaded in gray. Devil's-club grows in well-drained forests from coastal Alaska, southward and eastward to California, the Northern Rockies, and in a small population near northern Lake Superior.

Devil's-club rarely starts from a seed. If the seed germinates, the growth is slow. Instead, this dominant understory shrub expands by persistent clones that spread by stem elongation along the ground from which new stalks sprout (Lantz & Antos, 2002). **Figure 3** Tall plants topple, putting the stem in contact with the soil and new stalks grow in the form of large sprawling clones. This clonal system of expansion leads to thick groves of devil's-club, forming impenetrable thickets with plants reaching 4-6 meters in height (Burton & Burton, 2015). Despite the fortress created by these thickets, wildlife thrives because of the protection that *O. horridus* provides. The shade cover provided by devil's-club growing along the banks of streams

protect salmonoid fishes and their eggs. Grizzly, brown, and black bears inhabit these spaces because of the source of fish and their appetite for devil's-club berries, leaves, and stems (Howard, 1993). Brown and black bears are the dominant seed dispersers of devil's-club, which influences the introduction of new thickets in the forest (Harrer & Levi, 2018). Bears also have been known to use devil's-club as a medicine. A Tlingit of the organized village of Kake, Alaska witnessed two bears who seemed to chew devil's-club root to soothe their battle wounds (Justice, 1966).



Figure 3: Clonal expansion of *Oplopanax horridus*

Line drawings prepared by Catherine Jacobsen (Lantz and Antos, 2002)

2.3 Ethnobotany of *Oplopanax horridus*

2.3.1 Traditional Medicinal and Ritual Uses

The branches and inner bark of devil's-club are considered the most important medicinal bark preparation of the Pacific Northwest Coast region with ethnobotanical sources describing the root bark to be used as an antipyretic, antitussive, antibacterial, and report the extract of the inner root bark to contain hypoglycemic properties (Burton & Burton, 2015; Gottesfield, 1992; Johnson, 2006; Justice, 1966; Thommasen, Wilson & Mcllwain, 1990; Turner, 1982). The entire plant (leaves, stems, berries, woody material, and bark) covers an extensive range of ceremonial, technological, and medicinal uses. As told by oral myths, ethnographic

records and individual testimonies, the extract of the inner root bark was (and continues to be) used for a multitude of illnesses and diseases, including tuberculosis, cancer, and diabetes.

Written reports of devil's-club date from the late 1800s and are found in texts written by colonialist explorers and botanists. In 1896, outdoorsman and amateur botanist Martin Woodlock Gorman (1853-1926) wrote about the devil's-club he encountered while hiking near Yes Bay in southeastern Alaska that grew up to twelve feet high in wet canyons and along creek banks (Bornholdt, 2006). Gorman mentions that the Indigenous Peoples of the region would



Figure 4: Shaman's bundle made of spruce twigs, devil's-club roots, and a brown bear jaw that is tied with spruce root cord. Taken by G. T. Emmons before 1888 from a grave house on the Alsek River (Photograph by Richard A. Gould. AMNH.) (Emmons 1991).

use the young stems as food and boiled the bark to make a decoction that served as a medicine. Gorman also wrote that in "former times, the shamans or sorcerers (in Tlingit Sheh-shooh) chewed the roots, swallowing the juice, in the belief that it augmented their hypnotic powers." (1896, p. 73).

George Thornton Emmons (1852-1945), an ethnographer and photographer, wrote extensively of the Tlingit of the 1800s and early 1900s in a series of writings that were published long after his death in

1991. Emmons collected vast amounts of ethnographical data on the Tlingit of southeastern Alaska while serving in the United States Navy in the 1880s and 1890s. During his time off, Emmons would write detailed notes on his ventures throughout the land and recorded medicinal and ceremonial practices of devil's-club by the Tlingit. Emmons saw that devil's-club was used for external poultices, internal treatments, and ceremonial rituals (1991). Emmons wrote down specific details about the topical and medicinal

administration of devil's-club. These details give an accurate depiction of the past application of the plant as an external medicine and offer scientists clues as to how to prepare the bark to study in a laboratory setting. When used as an external poultice, the inner bark was cut into long strips, roasted, and pulverized in a layer of skin. The pulverized inner bark was then mixed with grease, and the gum of white pine then placed on affected areas of the skin to treat cuts, abscesses, sprains, and inflammations. Internally, the inner bark was boiled in water and used as an emetic and purgative. Emmons also recorded the ceremonial uses of devil's-club by shamans. **Figure 4** Initiate shamans would fast for days, chewing on the bark of devil's-club to reach contact with the spirit world. Shamans who had passed on to the next world were buried with bundles of devil's-club stalks under their heads. Bundles of devil's-club sticks and branches were hung above doors and windows to keep away the evil spirits of infectious disease.

James A. Teit, an early Canadian ethnographer and Indigenous activist who worked closely with Franz Boaz, recorded pages upon pages of information about the social organization, ceremonial life, customs, and belief systems of the Tahltan. Teit was born in Scotland's Shetland Islands and emigrated to British Columbia at the age of 19. He married a Nlaka'pamux woman and became well-versed in the Nlaka'pamux, Shuswap, and Lillooet languages. In his lifetime, Teit helped to form the Allied Tribes of BC organization and worked until his dying day for the protection of Indigenous land and their rights. In his meticulous findings, the medicinal preparation of devil's-club was explained in detail. According to Teit, the fresh stems of *O. horridus* were crushed and soaked in water to be drunk as a medicine for indigestion, stomach troubles, and used as a laxative, tonic, and a blood purifier. Another use was as an ointment. The stems were burned, and the ashes mixed with grease and the mixture

was then rubbed on swollen regions (1928, p. 459). Both Emmons and Teit were welcomed into the Indigenous communities who willingly provided intimate details of their medicinal and spiritual relationship with devil's-club, precious information that carries through to this day.

2.3.2 Cultural Keystone Species

Devil's-club [*Oplapanax horridus* (Sm.) Miq. (Araliaceae)] is a plant of great cultural import, considered to be a cultural keystone species for the Coastal and Interior Indigenous Peoples of British Columbia and Washington state (Lantz, 2001; Turner & Lantz, 2004; Turner, 2014). Garibaldi and Turner define a cultural keystone species as a “culturally salient species that shape in a major way the cultural identity of a people, as reflected in the fundamental roles these species have in diet, materials, medicine and/or spiritual practices.” (2004, p. 4). These species are intimately connected with Indigenous Peoples to such a degree that they depend upon the species to fulfill their needs for food, clothing, shelter, fuel, medicine, and holds spiritual significance. Cultural keystone species are deeply embedded in a People's cultural traditions and narratives, in ceremonies, dances, and songs and carry special meanings in their language.

Garibaldi and Turner identify cultural keystone species using the criteria: (1) intensity, type, and number of uses; (2) naming and terminology in a language; (3) symbolism and role in ceremonies and narratives; (4) persistence and collective memory of use in relationship to cultural change; (5) level of unique position in culture (difficult to replace with other species); (6) and range of resource acquisition beyond traditional territory (2004, p. 5). *O. horridus* has been used intensively and extensively by most tribes in the region of study, a concept that will be explored in length in this thesis. The medicinal use of devil's-club has been recorded to occur

across 38 linguistic groups throughout northwestern North America, revealing a direct correlation between the geographic distribution of the plant and its cultural usage (Lantz, Turner, & Swerhun, 2004). **Figure 5** The name of devil's-club in many Northwest Coast Indigenous languages reflects ancient elements from the Proto-Dene, Proto-Ts'mysenic, and Proto-Salishan language groups. Often its name recalls the sharp spines and thorns that adorn the plants' leaves and stems, finding their way under the skin when in contact. The Dene (Athabaskan) name translates as 'big thorn/spine.' The Nuxalk name for devil's-club (*tsk'alhkw*- "fir bark slivers") also refers to the sharp spines and slivers in relation to those associated with Douglas-fir bark (Turner 2014, p. 466).

Indigenous First Nations from Alaska, British Columbia, and Washington state have developed a timeless relationship with *Oplopanax horridus*. The Tlingit of southwestern Alaska continue to use devil's-club as a vital medicine and spiritual symbol of protection against evil and illness. The Nuxalk of British Columbia would boil the bark of the roots and stems and take the decoction as a purgative and to cure rheumatism (Smith H. I., 1927). Gottesfield and Anderson described the use of devil's-club in detail by the Gitskan People who live along the Skeena River of northwestern British Columbia. The inner bark of devil's-club is currently used by the Gitskan as a general tonic and for several ailments; rheumatism, respiratory disorders, for stomach ulcers and stomach pain, gynecologic cancers, and for open wounds. The Haisla (*χà'isla*- 'dweller's downriver') of the Douglas Channel along the north coast of British Columbia consider devil's-club to be their most important ritual and medicinal plant, using the root bark decoction to treat colds, rheumatism, arthritis, and cataracts. The Oweekeno of the Wannock River along the central coast of British Columbia regarded the decoction of inner bark as a

tonic, drunk daily to keep from getting ill and as a treatment for any form of sickness, especially colds, and aches and pains (Compton, 1993). The range of use (see **Figure 5**) extends far beyond these few communities mentioned, revealing the plant's deeply embedded place throughout the Northwest.

The therapeutic application of the root bark covers many illnesses and infections. Devil's-club root bark is administered usually as a poultice or internally. Fresh devil's-club inner bark was applied as a poultice to dress wounds and chewed for arthritis and in pre-hunting or fishing rituals. The inner bark, chewed up or heated, was used for external infections, cuts, burns, and sores as a poultice. The aqueous extract of the inner root or stem bark was also indicated to treat headaches, treat colds, fever, stomach troubles, sore throats, and the flu (Bloxtton & Marderosian, 2002). Other widespread uses of the decoction were as an emetic or as a laxative, for ritual cleansing of self, for a wash on hunting/fishing tools and clothing to mask the human scent, and as a charm to increase success in food procurement (Compton, 1993; Justice, 1966; Turner, 2014). The infusion (or decoction) of the stems, inner bark and wood was taken for several illnesses, including indigestion, rheumatism, arthritis, postpartum medicine, respiratory ailments, influenza, and generalized illness (see **Table 1**).

historians in personal journals, government reports, and ethnographic collections (Boas, 1932; Emmons, 1911; Gorman, 1896; Teit & Steedman, 1928). **Table 1**

Table 1: Medicinal uses of devil’s-club among some Indigenous Peoples of the Northwest Coast

People <i>(O. horridus name)</i> “translated”	Medicinal uses (literature references)
Gitksan <i>(wa’umst)</i>	The root and stem bark decoction were used as a purgative and as a diuretic, to treat gonorrhoea, to assist in the knitting of broken bones and was boiled, together with the entire plant of squashberry (<i>Viburnum pauciflorum</i> Raf.) for strangury and general illness (Smith H. I., 1927).
Haida <i>(ts’iilhenjaaw)</i>	A decoction of root and stem bark used to treat colds, sore throats, whooping cough, flu, fever, lung ailments, pneumonia, tuberculosis, rheumatism, arthritis, muscular disorders, and paralysis. Also used internally as a laxative and as a hair tonic (Turner, 1973).
Haisla	Devil’s-club bark was chewed or an infusion of the bark with seawater to act as a laxative and an emetic.
Northern Carrier	The inside layer of the inner bark was rolled into pills and ingested to treat cramps in stomach and bowel and was taken as a purgative with much hot water taken (Smith H. I., 1927).
Nisga’a <i>(wa’ums)</i>	The root bark was chewed to release a juice taken with a little water as a purgative. The root and stem bark were boiled and taken as a decoction to cure rheumatism. (Smith H. I., 1927).
Nlaka’pamux <i>(ka’tia)</i>	The fresh stems are crushed and soaked in water and drunk as a medicine for indigestion, stomach troubles. It also has laxative properties and is used as a tonic and blood purifier. Another use is as an ointment. The stems are burned, and the ashes mixed with grease, and this is then rubbed on swollen regions. (Teit and Steedman 1928, 459)
Nuxalk	The green inner bark is chewed for its emetic quality, and after vomiting, large amounts of water is drunk to cleanse. A steam-bath of devil’s-club was used to treat rheumatism and stomach troubles (Turner, 1973).
Oweekeno	A decoction of the inner bark of the devil’s-club from young spring growth is used as a tonic and used as a daily preventative against sickness, especially colds, rheumatism, and general aches and pains (Compton, 1993).
Southern Carrier	The bark was boiled, and 1-2 cups of the decoction were taken before and after childbirth as a purgative (Smith, 1927).
Tahltan <i>(khos chō / xwvs choo)</i>	“Of the many plants used for medicine, wild rhubarb root and the root and the stem of the devil’s-club are most freely used.” (Emmons 1911, 115)
Tlingit <i>(s’áxt’ / áchta)</i>	Used for cuts, abscesses, sprains, inflammations, and as an antiseptic. (Emmons, 1991)
Tsimshian <i>(wooms)</i>	Used in purification ceremonies and to bring good luck to hunters (Hudson, 1987).

2.3.3 Devil's-club specific for diabetes

Since diabetes first appeared in the Indigenous communities of the Pacific Northwest, physicians from British Columbia and Alaska published articles about the effect of devil's-club tea on blood glucose levels. Their patients testified that the tea was an effective medicine to treat their diabetes (Brockelesby & Large, 1938; Deagle, 1988; Justice, 1966; Macdermot, 1949; Thommasen, Wilson & McIlwain, 1990). Most articles that claim the hypoglycemic properties of the root bark reference the 1938 research trial conducted by Brocklesby and Large (Calway, et al., 2012; Justice, 1966; Smith, 1973). This trial presented evidence of the root bark extract lowering glucose levels in rabbits. Dr. Brocklesby became curious about the root bark's activity when a surgical patient who developed symptoms of diabetes upon hospitalization told him that he drank the infusion of the root bark for several years and was able to remain in good health without insulin. Later, Dr. MacDermot (1949) wrote of a patient who also drank the decoction of the root bark regularly. While the glucose levels of MacDermot's patient were still elevated, the patient testified that he felt well because of the tea. Dr. Darby (1949) of Bella Bella, a colleague of MacDermot, personally communicated to MacDermot that the Heiltsuk people in his neighborhood used the root infusion to treat their diabetes and regarded the infusion as a specific remedy.

Justice, a physician from southeast Alaska, also wrote of the many uses of devil's-club extract to treat various illnesses and conducted an experiment to test the hypoglycemic properties of the plant in two patients as many of his Tlingit clients regularly drank devil's-club tea for medicinal purposes. In 1988, Dr. George Deagle, a physician who practiced medicine for the Haida, published an article regarding Haida plant medicine as a valid and important source

of therapy in contrast to contemporary medicine that often fails in treating illness. In this article, Deagle testified that a patient who regularly drank the root bark infusion of devil's-club showed normal glucose levels in his blood. Dr. Thommasen (1990) declared that his Nuxalk patients used the infusion to treat their diabetic symptoms, and despite the negative results from his study on the effect of devil's-club extract on glucose levels, told Thommasen that they would continue to use the infusion as medicine after the conclusion of the study.

Ethnobotanists from British Columbia, Nancy Turner, Randy Bouchard, Trevor Lantz, and Leslie Johnson, have recorded through personal interviews and extensive research on the medical application of devil's-club root bark extract for diabetes (see **Table 2**). In these resources, the preferred method follows the way the man prepared the devil'-club in Hunt's transcription. The inner stem and root bark of devil's-club are scraped and boiled into a decoction and taken as a tea, one to three times a day. The use of a plant for medicine in the domestic sphere is a personal experience, where knowledge passed from elders reflect the value of a plant's medicinal activity used in sickness.

Violet Williams was a cherished elder and plant expert who was interviewed by Nancy J. Turner regarding her ethnobotanical knowledge of plants of the WSÁNEĆ people of the Saanich Peninsula near Victoria, British Columbia. Williams shared with Turner that she knew "a Quw'utsun' woman who was told she had diabetes and that she would have to take insulin injections every day. She decided instead that she would try taking traditional medicine, the *qwá7p-əlhch* (devil's-club) tea, and when she went back to the doctor for another blood test, the symptoms had disappeared." (Turner & Hebda 2012, p. 93). This little story may not hold

clinical significance yet provides evidence of the devil’s-club efficacy in treating symptoms of diabetes.

Indigenous People	Literature source
Cree	(Bouchard & Turner 1976; Marles, et al. 2000)
Metis	(Marles, et al. 2000)
Haida	(Lantz, Turner & Swerhun 2004)
Halkomelem	(Turner & Hebda 1990)
Nuxalk	(Thommasen, Wilson & Mcllwain 1990) (Turner N., 1973)
Nlaka’pamux	(Turner, Thompson, et al. 1990)
Secwepemc	(Ignace, Ignace, & Turner, 2016)
Squamish	(Bouchard & Turner 1976)
Sechelt	(Bouchard 1978)
Tsimshian	(Brockelesby & Large, 1938)
Straits Salish	(Turner & Hebda 1990)
Tlingit	(Justice, 1966)
Stl’atl’imx	(Lantz, Turner, & Swerhun, 2004)

Table 2: 13 Indigenous Peoples of the Pacific Northwest referenced to use the root bark of *O. horridus* in the treatment of diabetic symptoms.

2.4 Chemical and medicinal properties

As most Indigenous Peoples of the Pacific Northwest have used the devil’s-club plant for medicine, pharmacological studies have blossomed with scientists examining in the lab which phytochemicals may be responsible for the various sicknesses and diseases that have been treated by Indigenous health practitioners for millennia. Research trials of *Oplopanax horridus* report many biological and therapeutic qualities that can serve to treat serious diseases such as tuberculosis and cancer (Cheung, et al., 2015; Jang, Lee, et al., 2017; Jin, et al., 2014). All parts of the plant, the leaves, berries, and inner root and stem bark, have been used by Northwest Coast Indigenous healers. The inner bark of the root and stem of *O. horridus* was and continues to be used to treat numerous conditions, injuries, and diseases. While most pharmacological studies report medicinal activity using the powdered root bark in their studies; the leaves and berries of devil’s-club have also shown medicinal activity. The ethanolic extract of the leaves of

Oplopanax horridus have anti-oxidative and anti-inflammatory activities, attributes that are beneficial in the treatment of chronic diseases (Jang, Lee, et al., 2017).

Devil's-club is reported to have antibacterial, antifungal, antiviral, chemo-preventative, and antidiabetic activities. Research scientists Inui et al., Kobaisy et al. and McCutcheon et recorded antibacterial, anti-viral, anti-tuberculosis and antifungal activities. Kobaisy et al. (1997) identified five polyynes (organic compounds with alternating single and triple bonds) that exhibited antimycobacterial and antifungal activity. In their study, methanolic extracts of *O. horridus* inhibited the growth of *mycobacterium tuberculosis* and *mycobacterium avium*, the bacteria responsible for tuberculosis, along with the bacteria *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichi coli*, and *Pseudomonas aeruginosa*. The polyynes oplopandiol and falcarindiol were found to be the main compounds responsible for antimycobacterial activity in the extract. Inui et al. (2014) also studied the anti-TB activity of devil's-club using the biochemometric approach, in which they used countercurrent chromatography (CCC), *in vitro* biological evaluation of fractions, GC/MS analysis of fractions, and data analysis. In this analysis, Inui et al. identified four active phytoconstituents and 100 active principles against tuberculosis. McCutcheon et al. (1995) found that the methanolic extract of devil's-club inner bark showed partial inhibition of the respiratory syncytial virus, a sickness that causes infections in the respiratory tract and lungs.

Devil's-club has been used traditionally as a chemo-preventative with extracted compounds from *O. horridus* exhibiting anticancer activity in pharmaceutical investigations. The inner root and stem bark extract of devil's-club has shown antiproliferative activity on human ovarian, breast, colon and leukemia cancer cells (Li, et al., 2010; McGill, et al., 2014; Tai, et al.,

2006). Tai et al. (2006) recorded that the root bark showed antiproliferative activity against human breast and leukemia cancer cells. Hydrophobic constituents from the root bark extract was shown to have anti-proliferation activity in human breast cancer (MCF-7), human colon cancer (SW-480 and HCT-116) cell lines, and in an animal model of acute myeloid leukemia (Li, et al., 2010; McGill, et al., 2014; Sun, et al., 2010).

Several isolated compounds from OH explain the anti-proliferative activity against human cancer cell lines. Sesquiterpenes are a fascinating class of secondary metabolites that are produced by plants to deter predation and attract pollinators. The sesquiterpene nerolidol isolated from the root bark of devil's-club was found to inhibit the abnormal growth of cells in the large bowel. Extracts containing polyynes from the root bark inhibited proliferation of several breast, lung, ovarian, colorectal and lung cancer cell lines. Falcarindiol showed the strongest inhibition against the growth of all cancer cell lines in studies. Oplopantriol A, a polyne, showed antitumor and antiproliferative effects on human colorectal cancer cell lines (Zhang, et al., 2014). Li et al. tested the same polyne, Oplopantriol A, against multiple cancer cell lines, including leukemia and breast, revealing that the compound preferentially induces cancer cell apoptosis and proliferation (Jin, et al., 2014). Lastly, devil's-club extracted with ethanol was reported to have antiproliferation activity on pancreatic cancers, especially on the ductal carcinoma PANC-1 (Cheung, et al., 2015).

Chapter 3: Type 2 Diabetes

Type 2 diabetes is a complex metabolic disorder. This chapter is an overview of the biochemical origins of the disease with an emphasis on the contribution of systemic inflammation combined with postprandial hyperglycemia in causing diabetic complications and the subsequent treatment through the use of medications that inhibit the activity of digestive enzymes. The first section introduces the classification of the distinct types of diabetes and describes the pathophysiology and pathogenesis of type 2 diabetes. Insulin is the primary hormone responsible for signaling the uptake of glucose into most of the body's cells. This section defines the action of insulin, explains the mechanism of glucose uptake, and introduces the reader to the concept of glucose toxicity and the damage the condition causes. The middle section is devoted to describing how inflammation and the production of damaging chemical species (known as reactive oxidative species) lead to the destruction of integral body cells, including biomolecules (lipids, proteins, DNA) and pancreatic β -cells. Antioxidants found in food and medicinal plant sources halt the production of these damaging species, a relevant concept for the research I conducted with the root bark of devil's-club that measured the powerful antioxidant group of molecules known as polyphenols. The chapter concludes with describing the action of postprandial hyperglycemia in causing diabetic complications and the relevance of digestive enzyme inhibitors in controlling the rise of glucose levels in the blood following a meal.

3.1 Pathophysiology and pathogenesis of type 2 diabetes

3.1.1 Classification

Diabetes mellitus is a group of heterogeneous metabolic disturbances with a commonality in symptoms: muscular weakness and weight loss, excessive thirst and hunger, excessive urination, and a rise in blood glucose levels that, when the level exceeds the renal threshold, causes glucose to flood the urine (Marles & Farnsworth, 1995; Tentolouris, 2006). Diabetes is characterized by hyperglycemia, abnormally elevated levels of glucose in the blood. Insulin deficiency or dysfunction, abnormal fuel metabolism, and hyperglycemia cause the diabetic condition and can lead to serious complications and death if left untreated (Ortiz-Andrade, et al., 2007; Yki-Jarvinen & McClain, 2015). The various complications caused by prolonged hyperglycemia affect the entire body, especially the heart, the blood vessels, the eyes, the kidneys, and the nervous system.

Diabetes is generally classified into four groups: (1) type 1, (2) type 2, (3) other specific types of diabetes (including genetic defects that impair β -cell function or insulin action, diseases of the pancreas, and drug- or chemical-induced diabetes), and (4) gestational diabetes or diabetes that appears for the first time during pregnancy and generally resolves after the baby is born (Tentolouris, 2006). The two major classifications of diabetes, type 1 and type 2, share these common indicators: progressive death of β -cells, the cells that produce insulin in the pancreas, and, the lack of first-phase insulin release from the β -cells themselves (Bell, 2001). Type 1 diabetes (T1DM) is an autoimmune disorder usually occurring in juveniles that develops from a combination of genetic susceptibility and environmental factors. In T1DM, insulin

deficiency develops due to the cell-mediated autoimmune destruction of β -cells. A person with type 1 diabetes depends on insulin to survive.

Type 2 diabetes mellitus (T2DM) is a metabolic disorder in which abnormalities in insulin action and impaired insulin secretion cause the disturbances in glucose uptake. These abnormalities vary in proportion from person to person (or within the same person) during the course of the disease (Tentolouris, 2006). Several factors lead to the development of this form of diabetes. In type 2 diabetes, a combination of insulin resistance and insulin deficiency can cause ineffective glucose uptake (Makrilakis, 2006). In these cases, defective insulin secretion is insufficient to compensate for insulin resistance (decreased responsiveness to the action of insulin to stimulate glucose uptake in the tissues) and hyperglycemia develops. Another factor in defective secretion is when the insulin-producing β -cells in type 2 diabetic patients have both a decreased mass and number of insulin secretory granules. Glucose toxicity may also cause ineffective insulin secretion. Risk factors that increase the chances of development of T2DM are obesity, dyslipidemia, lack of physical activity and age (George, Augustine & Sebastian, 2014). T2DM is accompanied by pathophysiologic abnormalities and the progression of complications, including cardiovascular disease, neuropathy, and kidney disease (Muhammad Abdul-Ghani, 2015).

3.1.2 The pancreas: physiology of insulin and glucagon, glucose metabolism and homeostasis

After a person eats a meal, the healthy pancreas will release insulin directly proportional to the number of carbohydrates broken down. However, when the system goes awry, as in the case of type 2 diabetes, eating poses a threat to homeostasis as insulin no longer effectively

channels glucose effectively into cells. The pancreas is a complex organ, a gland that produces both endocrine (secretes hormones into bloodstream) and exocrine (secrete chemicals using glandular ducts) factors. This incredibly complicated organ secretes hormones that regulate the levels of glucose in the body while releasing digestive enzymes that break down ingested food into useable energy sources in the form of glucose. The pancreas releases hormones that work with each other to limit the release of glucose directly into the bloodstream in order to maintain a narrow range of glucose concentration in the blood. The human brain, a non-insulin dependent organ, requires glucose to function and lacks the ability to store glucose in its neurological cells. For this reason, the blood carries a level of glucose to flood through the brain to support proper functioning capabilities.

Insulin is a powerful peptide hormone with multiple actions that at the level of cells and tissues cause a cascade of responses, including the release of hormones and tissue factors that coordinate the function of multiple organs as a living being adapts to the nutritional environment (Langlais, Mandarino & Garvey, 2015, p. 164). β -cells are specialized cells found in the pancreatic islets of Langerhans that secrete insulin in response to glucose. The secretion of insulin is a dynamic process that is controlled primarily by the concentration of glucose in the plasma outside and inside the β -cells (Natali, Sterfano & Mari, 2015). **Figure 6** Insulin maintains blood glucose levels within a narrow range, ensuring glucose homeostasis despite fluctuations in food intake and periods of fasting. Once released into the blood plasma, insulin activates several signal transduction pathways, molecular reactions that convert a chemical or physical signal from outside the cell to a functional change within the cell. These changes result in

numerous effects within the human body, with the primary action being opening the gates for glucose to enter body tissues (excepting the brain, pancreatic, and red blood cells).

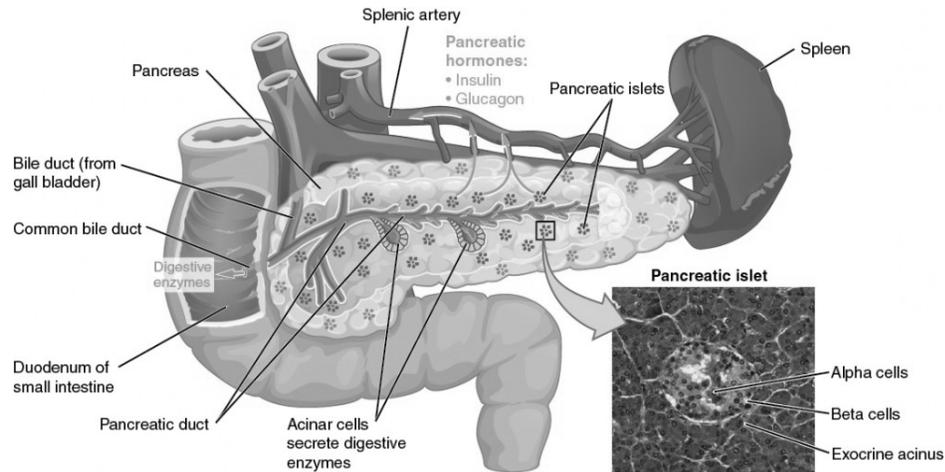


Figure 6: Pancreatic islets contain alpha (α) and beta (β) cells along with exocrine factors. Insulin (produced by β -cells) and glucagon (produced by α -cells) are the two integral hormones that regulate glucose metabolism. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

The secretion of insulin is regulated by the concentration of plasma glucose: an increase in glucose after a carbohydrate-rich meal causes an increase in the secretion of insulin. This response occurs in two phases after eating. The first phase is a short and small burst of insulin released once a person has ingested food- a response that happens quickly lasting only a few minutes. A more sustained, second-phase release of insulin occurs in direct proportion to blood plasma glucose levels (Seino, Shibasaki & Minami, 2015). Following the biphasic release, the elevated insulin (hyperinsulinemia) and glucose levels (hyperglycemia) stimulate the liver, gut, and muscle tissues to absorb the glucose. Insulin regulates glucose metabolism by tightly controlling glucose uptake, the synthesis of glycogen (a branched molecule or polysaccharide that contains glucose in a storage form which is released upon hydrolysis), and the release of

glycogen from the liver. About 25-50 % of oral glucose is taken up by the liver and stored as glycogen, and the rest is taken into muscle cells (80-85 %) and adipose tissue (10-25%) (Katsilambros, et al., 2006).

The α -cells of the pancreas produce glucagon, the hormone that breaks down the glucose-containing glycogen in the liver. Glucagon works directly with insulin to regulate glucose levels in blood plasma (Hædersdal S. , Lund, Knop, & Vilsbøll, 2018). Homeostasis depends on the delicate interaction between the hormones insulin and glucagon. The rise in glucose levels following a meal will stimulate the pancreas to release insulin and allows for the formation of glycogen, or glycogenesis, in the liver and muscles. The rise in insulin also suppresses the secretion of glucagon. Glucagon stimulates hepatic glucose production (gluconeogenesis) and inhibits the formation of glycogen (glycogenesis). If the level of glucose drops low, the state of hypoglycemia, the glucose-containing glycogen stored in the liver is released and broken down by glucagon. Glucagon suppresses the secretion of insulin in the state of hypoglycemia to ensure that the body's neurological system will not be starved of the important energy source.

After eating, glucose is transported via the bloodstream throughout the body and extracted from the blood by the brain, liver, red blood cells, skeletal muscles, skin, and fat cells with the help of a family of membrane-bound proteins known as glucose transporters (Loose, 2017; Ferrannini & DeFronzo, 2015). The plasma membrane is impermeable to polar molecules like glucose, and these carrier proteins embedded in the membrane bind and transfer glucose across the lipid bilayer. There are two classes of glucose carriers, Na^+ -glucose transporters (SGLTs) and facilitative glucose transporters (GLUTs). Unlike the SGLTs, the GLUT class of

glucose transporters consists of 14 types of proteins (GLUT1 – GLUT14) that are sodium and ATP-independent. GLUT2 takes up glucose into the β -cells where the glucose is metabolized to generate ATP (adenosine triphosphate), the main driver of insulin exocytosis into the bloodstream (Seino, Shibasaki & Minami, 2015). Increased ATP in the cytosol of β -cells causes

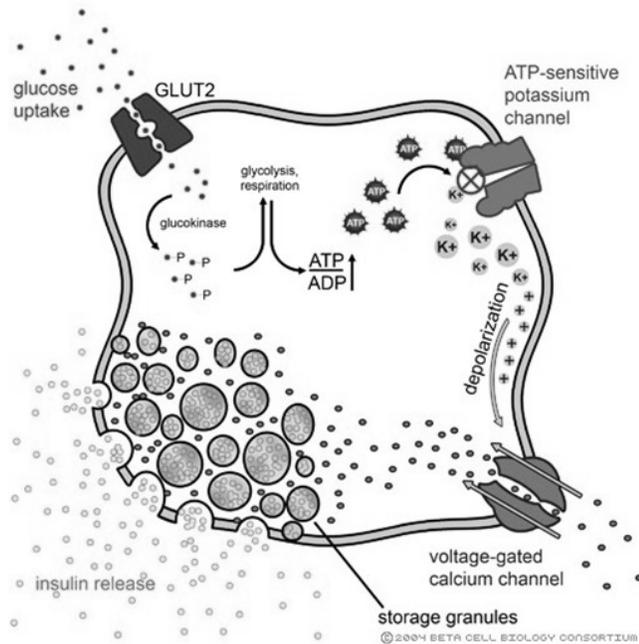


Figure 7: The secretion of insulin is induced by the diffusion of glucose via GLUT2 into the cytosol of a β -cell where the molecule is metabolized to generate ATP. The increased concentration of ATP then closes K_{ATP} channels, depolarizing the membrane to open calcium ion channels. The rise in Ca^{2+} induces the release of insulin from storage granules (Image provided by Beta Cell Biology Consortium (2001-2005), National Institute of Diabetes and Digestive and Kidney Diseases).

ATP-sensitive K^+ channels to close, depolarizing the plasma membrane and allowing for the voltage-dependent Ca^{2+} channels to open. The rise in intracellular Ca^{2+} triggers exocytosis of the insulin granules from the pools that store them. **Figure 7** The insulin-responsive glucose transporter, GLUT4, found in the heart, skeletal muscles, and adipose tissues, is responsible for the postprandial rise in plasma glucose levels (Wood & Trayhurn, 2003).

The hormone insulin performs several important tasks in the body to maintain homeostasis. Insulin not only regulates glucose, lipid, and protein metabolism; but also has important effects on the vascular function, the nervous system and the balance of electrolytes within the human body (Makrilakis, 2006). Insulin acts on lipid metabolism, stimulates protein synthesis and the transfer of amino-acids into muscles, inhibits platelet aggregation and causes vasodilation in small vessels while decreasing rigidity and stiffness of large arteries (Langlais, Mandarino, & Garvey, 2015). Insulin prevents death from ketoacidosis in type 1 patients and reduces the symptoms that accompany severe hyperglycemia in people with type 2 diabetes. Unfortunately, insulin does not prevent the chronic microvascular or macrovascular complication of diabetes as the hormone does not fully normalize glucose, or lipid and protein metabolism (Rizza, 2010).

3.1.3 Insulin resistance, glucotoxicity, and diabetic complications

From the previous section, the reader learned that insulin is the only hormone that counteracts hyperglycemia in the human body and that type 2 diabetes results from resistance to the action of insulin and insufficient secretion of insulin from the β -cells of the pancreas. Many of the body's tissues will never receive energy from the glucose molecule when the body's cells become resistant to insulin or if the cells that produce insulin become defective. Thus, the levels of glucose will rise in the blood. Clinical hyperglycemia can be divided into two categories, impaired fasting glucose, and impaired glucose tolerance. Impaired fasting glucose refers to an increased level of glucose (over 100mg/dL) in the blood when a person has not eaten or had anything to drink for a period of time, such as first thing in the morning after a night's rest. Impaired glucose tolerance (IGT) refers to a glucose reading taken after an oral

glucose test is administered. IGT is characterized by a two-hour post-prandial hyperglycemic spike measured at 140 mg/dL to 200 mg/dL (Rizza, 2010). Chronic hyperglycemia is the major risk factor for the development of microvascular diabetic complications in type II diabetics (Yki-Jarvinen & McClain, 2015). Post-prandial hyperglycemia, or the level of glucose in the blood within two hours of eating, contributes to endothelial dysfunction and cardiovascular disease (CVD) in humans (Arce-Esquivel, Bunker & Laughlin, 2011).

Hyperglycemia alters homeostasis within the body as glucose is the primary reaction molecule responsible for the production of the energy source, ATP. When glucose remains in the blood, the body is robbed of the energy products (ATP-- adenosine triphosphate) needed for healthy functioning of cells and organs. ATP is produced in cellular respiration, a biochemical process that uses glucose as the primary reaction molecule. In cellular respiration, the glucose molecule (in the presence of oxygen) is broken down to produce the energy fuel molecule, ATP, and the waste products, carbon dioxide and water. This process occurs in four stages (see **Figure 8**). In the first stage, the glucose molecule is split (glycolysis) in the cytoplasm of the cell, producing two molecules of pyruvic acid, or pyruvate, and two ATP molecules. In the next stage, the pyruvic acid is transported into the mitochondria (with the help of carrier proteins) where the pyruvic acid is converted to Acetyl-CoA (acetyl coenzyme A). The third and final stages of cellular respiration take place in the mitochondrial matrix and involve the complex biochemical conversion (Krebs cycle or citric acid cycle) of Acetyl-CoA into 34-36 ATP molecules and the byproducts of respiration, water, and carbon dioxide. Glucose that remains in the blood starves the body of this necessary molecule needed to produce energy, possibly

leading to dementia, memory loss, and insulin deficiency in skeletal muscles in diabetic patients (Federation of American Societies for Experimental Biology, 2019; Karakelides, et al., 2007).

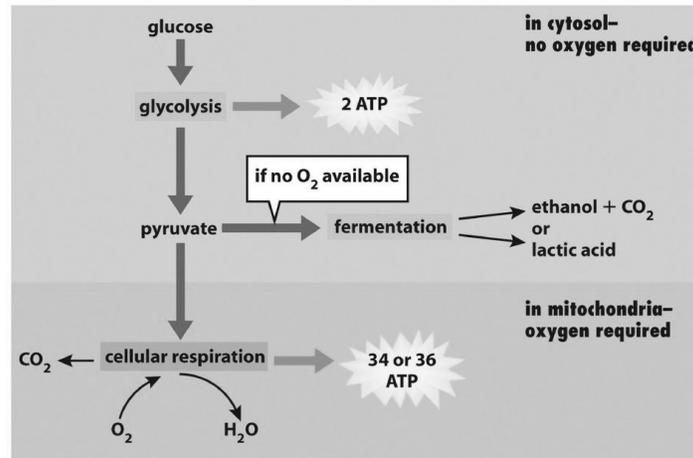


Figure 8-1 Biology: Life on Earth, 5/e
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Figure 8: In cellular respiration, the glucose molecule (in the presence of oxygen) is broken down to produce the energy fuel molecule, ATP, and the waste products, carbon dioxide and water.

Chronic high levels of glucose can lead to a condition known as glucose toxicity or glucotoxicity, a major contributor in the development of insulin resistance and impaired insulin secretion in type 2 diabetes. Extracellular glucose is toxic to β -cells, the pancreatic endocrine cells responsible for the secretion of glucose. Pancreatic β -cells maintain glucose homeostasis by secreting insulin in response to change in extracellular glucose. Rosseti et al. (1990) reported that prolonged exposure of β -cells to high levels of glucose impairs insulin gene transcription resulting in a metabolic loss of the first burst of insulin right after eating. This decrease in insulin production causes postprandial hyperglycemia, a major contributor to the increase in cardiovascular-related complications in those with T2M (Bell, 2001). Further, the chronic exposure of β -cells to high glucose concentration leads to dysfunction and death of β -cells due

to oxidative stress and oxidative damage as well as insulin resistance at the level of the cells (Wu, et al., 2004; Yki-Järvinen & McClain, 2015). Beyond the pancreas, glucotoxicity causes damage throughout the body's systems. As discussed earlier, there are non-insulin and insulin-dependent tissues throughout the human body. In non-insulin-dependent tissues (i.e. the kidney, retina of the eyes, peripheral nerves), the chronically elevated glucose levels surrounding the tissues cause microvascular damage to the vessels and lead to severe complications (Yki-Järvinen & McClain, 2015).

People with diabetes have double the risk of death compared with healthy people due to the number of disabling and life-threatening complications that accompany the disease (Chávez-Silva, 2018). The list is long. Cardiovascular disease (CVD), chronic kidney disease, blindness, lower-limb complications, gastrointestinal degeneration, neuropathy, are some of the morbid complications that lead to the high morbidity and mortality of the disease when the glycemic levels are not held in check (Koye, Magliano, et al., 2018). Diabetic foot ulcers are one of the most common complications of diabetes in the lower extremities. These ulcers are the most important risk factor for lower-extremity amputations. Vascular diseases, foot deformities, minor trauma, peripheral neuropathy, and a history of ulceration or amputation are all risk factors for ulcer development. In people with diabetes, wound healing does not move easily beyond the inflammation stage which impairs the healing process.

Insulin resistance, hyperglycemia, and the associated glucotoxicity adversely affect the entire body's metabolism and is associated with an extensive list of moderate to severe complications, including kidney failure, liver and brain damage, loss of skeletal muscle tissue, and eye disease (Gupta, et al. 2016). Type 2 diabetes results from resistance to the action of

insulin and insufficient secretion of insulin from the β -cells of the pancreas. Insulin resistance is related to obesity, especially abdominal or visceral obesity. However, insulin resistance is not solely associated with adipose areas. Triglyceride concentration in non-adipose areas or the shift of lipid deposition from adipose tissue to non-adipose tissue like muscle and liver cells is also related to insulin resistance (Makrilakis, 2006). Several epidemiological studies and clinical trials have shown that hyperglycemia can lead to coronary artery disease, renal failure, blindness, limb amputations, cerebrovascular disease, neurological complications, and early death (Ortiz-Andrade, et al. 2007). Lastly, fasting and postprandial hyperglycemia are associated with the deterioration of endothelial function and atherosclerosis due to increased inflammation and oxidative stress (OS), increasing the risk of ischemic heart disease in people with type II diabetes in patients with diabetes mellitus (Djindjic, et al. 2017; Gerstein, et al. 2014).

3.2 Inflammation, reactive oxygen species, and the power of antioxidants

Chronic hyperglycemia leads to high levels of oxidative stress due to the overproduction of reactive oxidative species (ROS), free radicals that are characterized by one or more unpaired electrons. These unpaired electrons are highly reactive with other molecules in the human body. Excessive levels of ROS overload the body's antioxidant defensive abilities, leading to a state called oxidative stress. Oxygen free radicals are normal byproducts of cellular metabolism. A low concentration of these oxidated species are actually beneficial due to their physiological ability to defend against infectious agents and as well as their role in cell signaling systems. (Valko, et al., 2007). The body has a defense mechanism to protect against oxidative stress in the class of enzymes known as antioxidants. However, when the concentrations of oxidative

species rise in the body, the antioxidative defenses are overwhelmed leading to an overproduction of free radicals. These free radicals cause damage due to irreversible chemical bonds they form with the body's proteins and cascade interruptions in cell signaling processes. Oxidative stress has been implicated in the onset of chronic diseases, including diabetes, as it causes damage to biomolecules (lipids, proteins, and DNA), tissue, and organ cells (Govindaraj & Pillai, 2015; Pirian, et al., 2017).

Persistent hyperglycemia depletes antioxidant levels in the body, causing superfluous free radicals to circulate and the complications of diabetes arise (Govindaraj & Pillai, 2015). Recent studies demonstrate that overproduction of the oxidant, superoxide, in cellular respiration induced by hyperglycemia seems to be the key event in the activation of all other oxidative stress pathways involved in the pathogenesis of diabetic complications (Ceriello, et al., 2006). When blood glucose levels rise rapidly, and lipid levels are high, reactive oxygen species are generated to a toxic level. Pancreatic β -cells are especially susceptible to ROS toxicity as they do not possess a defense system capable of reversing oxidation at excessive levels. Chronic oxidative stress results in defective insulin gene expression, insulin secretion and the increased β -cell apoptosis that leads to the deterioration of these cells. Prolonged hyperglycemia also leads to the development of advanced glycated endproducts (AGEs), reactive species that contribute to the microvascular, macrovascular, and tissue damage in diabetic patients (Tibaut & Petrovič, 2016).

Postprandial hyperglycemia (the level of blood glucose within one to two hours of eating) stimulates reactive oxygen species production causing oxidative stress, leading to postprandial inflammation and endothelial dysfunction. The endothelium is the innermost layer

of blood vessels responsible for regulating vascular tone and structure. An important function of the endothelium is to provide adequate blood supply to the body's different tissues, a process regulated by vasodilators and vasoconstrictors, and provide a conduit for the immune system to fight infection via inflammatory signaling. Inflammation is a normal immune response to infection or injury that increases vascular permeability to immune cells that over time causes the body to attack its cells. In type 2 diabetes, chronic low-level inflammation of the adipose tissues leads to insulin resistance in body tissues (Grandl & Wolfum, 2018). Chronic exposure to stressors like inflammation, oxidative stress, and hyperglycemia causes the endothelium to change and leads to endothelial dysfunction, the cause of microvascular complication in type 2 diabetes (Arce-Esquivel, Bunker & Laughlin, 2011).

The oxidation of glucose and lipids along with the non-enzymatic glycation of proteins leads to the formation of free radicals, thus promoting oxidative stress and the development of insulin resistance (Joshi, Lad, Sharma, & Bhatnagar, 2018). Antioxidants are a primary line of defense against oxidative damage due to their ability to scavenge free radicals from reactive species among other redox properties (singlet oxygen quenching and metal ion chelation) (Stankovic, Niciforovic, Topuzovic, & Solujic, 2011). Naturally occurring antioxidants in foods and plant medicines offer an external source for balancing the effects of reactive oxidative ill effects within the body. Phenolic compounds, including polyphenols, are chemicals formed as secondary metabolites to defend plants against disease and oxidative stress. Plant polyphenols reduce oxidative stress in experimentally induced diabetes mellitus and do not have the side effects that many diabetic medications cause in those patients who take them. Jang et al. (2017) investigated the anti-oxidative properties of the ethanolic extracts of the leaves, stems,

and roots of devil's-club. The extracts exhibited anti-oxidative activity in numerous tests, including radical scavenging, reducing, and inhibition of lipid oxidation powers. In this study, I examined the quantity of polyphenols in the root bark extracts of devil's-club with the understanding that the phenols contained within the extract help to reduce the inflammation caused by oxidative stress from prolonged hyperglycemia.

3.3 Post-prandial hyperglycemia and inhibition of digestive enzymes as therapy

3.3.1. Post-prandial hyperglycemia

Post-prandial hyperglycemia is the rapid rise in glucose levels that occurs right after a person with diabetes ingests a meal. Higher postprandial hyperglycemia is associated with increased mortality due to cardiovascular problems, higher incidence of major cardiovascular events like myocardial infarctions and stroke, and the progression of retinopathy (Ceriello, et al., 2006; Gerich, 2003; Mannucci et al., 2012).

Cardiovascular harm is caused by oxidative stress, impaired endothelial function, and overexpression of adhesion molecules that follow prolonged periods of elevated blood glucose after eating (Mannucci, Monami, et al., 2012). One of the primary recommendations in controlling diabetes is to maintain tight or strict glycemic control, the act of keeping blood glucose levels within the normal range without serious drops in levels to cause a state of hypoglycemia.. The Diabetes Intervention Study showed that postprandial, not fasting glucose, hyperglycemia was an independent risk factor for cardiovascular disease (CVD), retinopathy, myocardial infarction and cardiac death (Bell, 2001; Djindjic, et al., 2017; Takao, et al., 2017). Strict glycemic control of postprandial hyperglycemia can prevent these macrovascular

complications, reducing the risk of developing associated diseases as fluctuations of blood glucose play a pivotal role in the pathogenesis of micro- and macrovascular complications.

As learned in the previous section, postprandial hyperglycemia leads to the production of free radicals and oxidative stress, causing endothelial dysfunction, reduction of myocardial blood flow, and inflammation. The STOP-NIDDM trial showed that treatment of subjects with impaired glucose tolerance with the α -glucosidase inhibitor acarbose was associated with a 36% reduction in the risk of progression to diabetes and a 34% risk reduction in the development of new cases of cardiovascular events, such myocardial infarctions (Ceriello, et al., 2006). Correcting postprandial hyperglycemia is an elite strategy to prevent and manage cardiovascular disease and other vascular complications in diabetes (Ceriello, et al., 2006).

3.3.2 Diabetes treatment: individual self-management and medications

Type 2 diabetes is a preventable disease. People who receive effective clinical care and carefully control their glycemic levels, blood pressure, and lipid and stress levels, through self-management can live healthy and productive lives (Maar, et al., 2011). Obesity, diet, and negative lifestyle behaviors contribute to a person developing type 2 diabetes. The endocrine organ adipose tissue influences the metabolism of glucose and lipids by releasing free fatty acids and proinflammatory factors, adipokines; both of which impair glucose metabolism, promote the synthesis of toxic metabolites and alter the signaling of insulin (Gastaldelli, Gaggini and Defronzo, 2017). A diet consisting of excessive carbohydrates contributes to hyperglycemia as these starches are quickly digested by pancreatic enzymes into simple sugars, like glucose or fructose.

For the populace to have a good chance of avoiding diabetes, certain factors are important. These include the suitability of the outdoor environment for activity and sport; access to healthy food and drinkable water; education on healthy choices in schools; implemented prevention policies; and accessible information on healthy choices (Zimmet, 2014). Negative lifestyle behaviors, including smoking, excessive eating and lack of exercise, greatly increase the risk of developing type 2 diabetes. Consumption of processed foods, especially those with high fat and sugar content, is a common contributing factor combined with a sedentary lifestyle with little to no exercise. Modern lifestyles are characterized by quick and easy meals that are highly processed and rich in refined carbohydrates, fats and sugars, and sedentary living with minimal physical activity. A close look at what types of foods predispose people to type 2 diabetes is a good idea when advising lifestyle changes in the form of diet modification.

Physical activity and a controlled diet protect against type 2 diabetes, helping to reduce obesity and the complications that accompany excessive weight gain while improving the quality of life among those that are physically active (Hemmingsen, 2017; Roberts, Butler III and Green, 2016). The best way to prevent the deleterious effects of hyperglycemia in type 2 diabetes is to control glucose levels in the blood. Glucose enters the circulatory system because of the hydrolysis of carbohydrates by digestive enzymes, like α -glucosidase and α -amylase. α -glucosidase is secreted by brush border cells in the small intestines where it hydrolyzes polysaccharides. α -amylase is secreted by the pancreas and salivary glands and hydrolyzes starches and oligosaccharide into simple sugars. The inhibition of these digestive enzymes can

reduce the levels of glucose in the blood after eating carbohydrates and is a therapeutic approach for managing diabetes (Kalita, et al., 2018).

In the Western model of treatment for diabetes, dietary and lifestyle interventions are considered the most important intervention for patients with type 2 diabetes. Diabetes therapy is predicated on the patients' willingness to control glucose levels with medication and personal practice of healthy nutrition and physical activities that promote weight loss. Carbohydrates that absorb slowly and a diet rich in fiber help to keep post-prandial glucose levels low. Many diabetic patients struggle with the strict regimen of diet and exercise and fail to achieve tight glycemic control. When diet and physical exercise alone are not successful in modulating blood glucose levels, medications are prescribed to reach targets (Leroux-Steward, Rabasa-Lhoret and Chiasson, 2015). Oral hypoglycemic medications are often prescribed to assist in the tight glycemic control necessary to halt the progression of the disease. α -Glucosidase inhibitors (AGI) delay the digestion of complex carbohydrates, decrease the postprandial rise in blood glucose, and mimic the effect of a low glycemic index/ high-fiber diet (Leroux-Steward, Rabasa-Lhoret and Chiasson, 2015). A great number of resources for medicine, nutrition, physical training, and medical care is expended on the treatment and management of type 2 diabetes to treat prolonged hyperglycemia and the complications that follow. Insulin is prescribed in cases when behavioral modification and oral hypoglycemic agents are unable to lower glucose levels. In Indigenous communities, the positive support of the family and community is crucial in managing the disease.

3.3.3 The inhibition of digestive enzymes as therapy

α -Glucosidase inhibitors (AGIs) are oral glucose-lowering drugs that delay the digestion of complex carbohydrates and decrease postprandial glucose levels due to their effect at the intestinal absorption level. These inhibitors block the action of α -glucosidase digestive enzymes in small intestine border cells. The primary activity of these digestive enzymes is the hydrolysis of polysaccharides (oligo- or di-saccharides) to monosaccharides to facilitate the absorption of monosaccharides into the small intestine's brush border cells. The inhibition of α -glucosidases delays the intestinal absorption of carbohydrates at the small intestine and retards glucose from entering systemic circulation, thus decreasing the glycemic index of carbohydrates. AGIs improve the sensitivity of insulin in cells and reduce stress caused by glucotoxicity in insulin-producing beta-cells (Gupta, et al., 2016).

Acarbose, miglitol, and voglibose are the most commonly prescribed AGI to type 2 diabetic patients. Acarbose slows the digestion of carbohydrates by to slowing down the breakdown of carbohydrates in the gut and delaying the absorption of carbohydrates, thus reducing post-prandial hyperglycemia (Li, Fu, et al., 2016). Lowered blood glucose concentration is accompanied by a decrease in insulin sensitivity. As hyperglycemia is the contributory factor in the development of microvascular and macrovascular complications, this medication can lower the risk of developing these complications. Acarbose combined with insulin therapy has been shown to reduce oxidative stress and inflammation in patients with T2DM (Li, et al., 2016). Side effects of acarbose include abdominal pain, bloating, diarrhea and flatulence, because of increased amounts of carbohydrates delivered to the intestine (Upadhyay, et al., 2018)

Miglitol, unlike acarbose, is absorbed and then excreted by the kidneys. This α -glucosidase inhibitor has been shown to decrease glucose fluctuations in T2DM patients recently diagnosed with acute coronary syndrome, a condition that is caused by decreased blood flow to arteries in the heart (Kitano, et al., 2013). Voglibose decreases post-prandial hyperglycemia, yet, like acarbose, causes uncomfortable gastrointestinal side effects. All three α -glucosidase inhibitors are effective in reducing postprandial hyperglycemia, but many patients stop taking the medication because of the adverse side effects (Upadhyay, et al., 2018). Plant-based medicines and functional foods are valuable sources in the research of new medications that may act as α -glucosidase and α -amylase inhibitors.

Chapter 4: Methodology

4.1 Ethnopharmacological methodology

Plant selection

Devil's-club was selected as the primary plant of study due to the root bark being used to treat symptoms of diabetes by multiple Pacific Northwest Indigenous communities. I first read about the diabetic activity of devil's-club root bark when the plant was referenced on the world-wide-web using the search terms "plant," "diabetes," and "Pacific Northwest." In researching the literature, I found multiple sources that described the root bark's medicinal efficacy as well as centuries-old texts that spoke of the plant in myths and recorded oral traditions. These searches led me to the questions that directed my thesis: Does the root bark extract of devil's-club have a hypoglycemic effect and do oral tradition and ritualistic practices of Pacific Northwest Indigenous peoples foretell the medicinal activity of the root bark? There were few scientific studies in the literature that specifically tested for this bioactivity and I chose to design my research program focusing in on identifying antidiabetic capabilities within the plant for the chemistry component of my thesis. Following a methodology based in ethnopharmacology, I brought specimens of *Oplopanax horridus* into the lab and conducted a series of tests to explore possible hypoglycemic actions within the root bark.

The habitat of devil's-club is the wet areas of deep forest floor and required care in gathering specimens to ensure that surrounding flora was not disturbed. There were two collections of the roots, stalks, and stems of *Oplopanax horridus* that took place over the course of two years during the months between December and March. Sites were chosen on the basis

of the size of grove and ease of entry due to the thorns and wet ground. Most of the specimens were collected in the lowland areas of the reserve and on the banks of creeks. I obtained an exact botanical identification of the plant by referencing botanical texts and consulting a local herbal specialist on Lummi Island, Washington.

The inner root bark of the stems and barks of *Oplopanax horridus* was used as the primary source of plant matter to be researched due to its medicinal significance in Indigenous research in the treatment of illness and disease. Bark from trees and shrubs are widely used in medicinal preparations worldwide, being a source of pharmaceutical drugs. Like human skin, plants have layers that protect and provide vessels that bring nutrients throughout the plant's system. The bark is the woody outermost layer of a root or stem. In the preparation of devil's-club stem and root, the outermost layer containing thorns and woody layer is scraped away. According to Carla Burton (2012), in her dissertation "Using Plants the Nisga'a Way: Past, Present, and Future Use", devil's-club root is the preferred medicinal portion of the plant and it is meant to be harvested after the leaves have fallen off in the fall and winter. The Gitskan use the inner bark or cambium layer to be scraped off to be prepared for medicinal purposes (Johnson-Gottesfield and Anderson, 1988). Violet Williams and Elsie Claxton of the Nlaka'pamux (Southern British Columbia and North Cascades, Washington) shared that the medicine within the bark is contained in the soft, moist, and light-colored portion of the bark, or the inner bark, and not the hard, usually darker outer bark (Turner & Hebda, 1990, p. 68). With this valuable information, I used the soft inner portion of the bark in all tests conducted in the lab.

The use of devil's-club as medicine is indicative of a rich and knowledgeable Indigenous system of health treatment in the sociocultural context of the people who used the plant in the

past (Genuisz, 2009). The collection of ethnobotanical data of *Oplopanax horridus* was conducted by a thorough review of the literature and via personal correspondence with Dr. Nancy J. Turner (ethnobotany, University of Victoria), Dr. Dana Lepofsky (archeology, Simon Fraser University), Brian Carpenter (curator of Native American Materials, Center for Native American and Indigenous Research), Benoît Thériault (Collections Information Specialist, Textual Archives Canadian Museum of History), Dr. Judy Thompson, Edōsdi- (First Nations Studies, UNBC), and Elizabeth Watanabe (tribal liaison for Washington Health Care Authority).

4.2 Methods

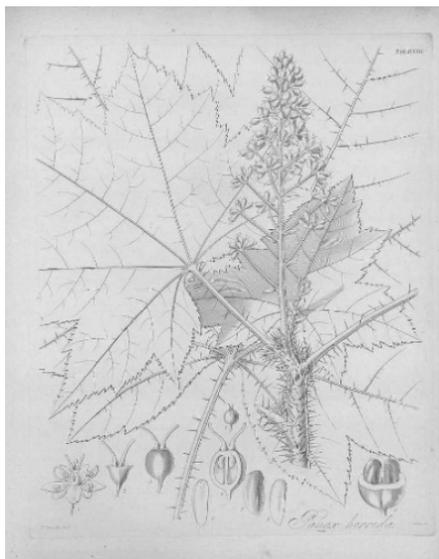


Figure 9: *Oplopanax horridus* lithograph by W.J Hooker in *Flora boreali-americana*, circa 1840.

The active research in this program began in a Pacific Northwest forest reserve where I harvested the root bark and ended in the labs of Dr. Vyvyan (WWU, organic chemistry), Dr. Spiegel (WWU, biochemistry) and Exact Scientific Labs Inc. (Ferndale, Washington) where I tested the root bark using bioassays in three separate experiments. The first phase of research involved the identification of *Oplopanax horridus* (see **Figure 9**) and the gathering of the fresh roots from the forest floor. In the autumn months of 2015, I obtained a permit from the Washington State Department of Natural Resources to gather devil's-club plant specimens from The Lake Louise NRCA (Stimpson Family Nature Reserve) in Whatcom County, Washington. After gathering the specimens, I returned to the Vyvyan Research lab at Western Washington University to prepare the bark for extraction. In the second phase of research, I stripped the inner root bark of the rough outer bark and dried the bark for two weeks, following the traditional method of the Indigenous Peoples of the Pacific Northwest. The third phase began

with grinding the root bark to a fine powder. This medicinal powder was extracted using the Soxhlet extraction method with a series of five solvents (hexanes, dichloromethane, ethyl acetate, acetone, and methanol). The final stage was the most crucial in my research program in which the five extracts were subjected to biochemical examination using three different tests. The phytochemical analysis and interpretation of these tests accounted for antioxidant activity and inhibitory activity against α -amylase and α -glucosidase at various concentrations. The Experimental section following this chapter describes the details of the final phase, including results and discussion.

4.2.1 Literature Review

Search Methods

I searched multiple databases for the literature review, including EBSCO, JSTOR, ProQuest, PubMed, SciFinder Scholar, and Web of Science, using the following outcome terms: type 2 diabetes, mortality, morbidity, macrovascular complications, microvascular complications, postprandial hyperglycemia, Lummi, Salish, Coast Salish, Haida, Tsimshian, oral traditions, oral mythology, *Oplopanax horridus*, Devil's-club, advanced glycation end-products (AGEs), α -amylase, α -glucosidase, antioxidant, digestive enzyme inhibition, decolonizing ethnobotany, polyphenols, Folin-Ciocalteu phenol, microaggressions and diabetes, traditional foods, Indigenous Knowledge, Indigenous peoples and diabetes, prevalence diabetes indigenous peoples, decolonization, Indigenous Research methodology, Indigenous Knowledge Systems, cultural keystone species, and Traditional Ecological Knowledge.

Research trials in the bioactivity of *O. horridus*

As discussed in Chapter 2, Indigenous Peoples of the Northwest Coast have used *Oplopanax horridus* to treat multiple chronic and acute illnesses and diseases (tuberculosis, cancer, diabetes, etc.), many of which have been formally researched by scientists worldwide. These pharmacological studies report that *Oplopanax horridus* possesses several biological and therapeutic qualities, including antibacterial, anti-arthritis, antifungal, anticonvulsant, antiproliferative (cancer cell lines), and antidiabetic capacities (Calway, et al., 2012; Kobaisy, et al., 1997; Jang, et al., 2017; Jin, et al., 2014; Wu, et al., 2018).

Dr. Chun-Su Yuan and his group of scientists at the University of Chicago have conducted several studies about *Oplopanax horridus*. Yuan et al. have isolated several compounds from *O. horridus* and have tested these constituents for antifungal, antioxidant, anticancer and antidiabetic activities. Yuan et al. isolated polyynes (polyacetylenes), phenylpropanoids (aglycones and glycosides), lignan glycosides, triterpenoids, sesquiterpenes, and volatile compounds (Huang W.-H., Zhang Q.-W., et al., 2014). Of these compounds, the polyynes have been reported as potential anticancer and antimycobacterial natural products (Wu, Wang, Yuan, & Huang, 2018). These polyynes, characterized by a long chain of carbon atoms with alternating double and triple bonds, are unsaturated hydrophobic compounds that are found in high concentration in the roots. To date, the polyynes Oplopantrial A and Falcorindiol have shown the highest inhibition on the growth of cancer cell lines investigated in the labs of Yuan and Jin et al. (Jin, et al., 2014; Jin, et al., 2012).

Experimental studies in diabetes

“Our attention was brought to this material through the examination by one of us of a surgical patient, who, on hospitalization, developed marked symptoms of diabetes. This person, it was learned, had kept in apparent good health by oral doses of an infusion of this root bark, and is in fact still leading a normal life with the aid of this infusion.” (Brockelesby and Large 1938, p. 32)

Brocklesby and Large

In 1938, scientists Brocklesby and Large tested white Belgian rabbits with biological assays to determine if the roots of Devil’s-club contained a hypoglycemic substance. After starving rabbits for 24 and later 48 hours, glucose levels of the rabbits were recorded and tested against devil’s-club extract with the control receiving no extract. The extract was prepared from the fresh or dried bark of the roots of devil’s-club and made into an infusion with hot water. Brocklesby and Large presented data that showed the extract exhibited marked hypoglycemic properties in the starved rabbits (1938).

Justice

Dr. Justice (1966) was curious about devil’s-club because of the number of patients he spoke to who used the medicine. He interviewed his patients on their use of the extract, talking to members of the Haida, Tlingit, and Tsimshian in the southeast Alaskan villages of Yakutat, Hoonah, Kake, Klawock, Hydaburg, and Metlakatla. His informants used the extract as a general tonic and to treat and relieve the pain of a number of maladies: like a toothache, finger infection, Hodgkin's disease, arthritis, ax wound, cancer, and diabetes. To test the efficacy of the plant, Justice studied two persons, a 72-year-old Native American female and a 32-year-old white male, who agreed to take glucose tolerance tests before and after taking devil’s-club

extract. The female subject regularly drank devil's-club extract, while the male had never taken the extract. After the glucose tolerance test, the results did not show any marked effect on glucose levels with or without extract. The male subject did experience diarrhea and "the effects of hypoglycemia" (Justice 1966, p. 37). Justice concluded that the reaction in the male did confirm the animal experiments of the Brocklesby and Large study. Justice also affirmed that the use of devil's-club extract to enhance the ability of the shaman to enter a trance-like state was related to a hypoglycemic effect.

Thommasen et al

Physicians Thommasen, Wilson, and McIlwain (1990) tested the hypothesis that devil's-club tea taken on a short-term basis can significantly lower blood glucose levels. Two human adults diagnosed with diabetes ingested devil's-club tea to attest the hypoglycemic activity. Their diet, activity, clinical condition, and blood glucose levels were closely monitored. The male patient, 39 years of age, was a type 1 diabetic dependent on insulin for survival. The female patient, 79 years of age, was newly diagnosed with type 2 diabetes. The control group consisted of two healthy people, a female and a male both 30 years of age. The diabetic male was subjected to abstain from taking insulin for the duration of the test and his glucose levels rose steadily, despite his use of devil's-club tea. The patient was to go one day without the tea, and one day with the day. Both days, the doctors noted a rise in blood glucose and ketone levels. The patient's subjective experience was that on the day he was able to drink the devil's-club tea, he felt "fine", with little symptoms but thirst and fatigue at the end of the day (Thommasen, Wilson and McIlwain, 1990). On the day he received no tea and no insulin, the patient complained of a pounding heart, thirst, lack of energy, muscle pain, nausea, and

vomiting. The woman with type 2 diabetes showed a steady decrease of blood glucose levels to normal range, but the doctors stated the drop in glucose took place before she began to drink the tincture and when she ceased to take the tea. The graph that reads the glucose levels does show a pattern of glucose normalization with fewer dips and peaks in the levels, suggesting the tea did modulate blood glucose level. The two healthy patients experienced nausea, light-headedness, and vomiting. Thommasen stated these symptoms were not related to hypoglycemia, but the extract itself. He concluded that the plant shows no hypoglycemic activity.

4.3.2 Background: Medicinal Plants

Medicinal plants are a class of plants applied for therapy and/or possess pharmacological properties for humans and animals (Kusuma, et al., 2014). Much of the world's population value medicinal plants in treating the daily sicknesses and chronic diseases from which they suffer. Healing plants are usually readily available as they grow near the people who use them and are a valuable form of medical treatment with little to no cost. Medicinal plants contain molecular compounds, bioactive constituents, that have important biological and pharmacological activities; e.g., anti-inflammatory, anti-depressant anti-oxidative, antibiotic, hypoglycemic, and anti-carcinogenic (Heilmann, 2009). These active principles, or phytochemicals, exist for any known biological activity of a given plant (Inui, et al., 2012).

Phytochemicals are ecological mediators of interrelationships between humans and plants, serving to treat disease and discomforts in the human system since people first gathered plants for medicine (Bannister, 2000). Complex natural products, like those found

within the plant parts of *O. horridus*, contain a great number of secondary metabolites, the active constituents in plants responsible for biological activity in humans. Secondary metabolites are phytochemicals that have no metabolic function in plants. Instead, they serve as chemical defenders against herbivores and pests and attract pollinators and seed dispersers, like birds and butterflies (Spurlin, 1997). Secondary metabolites have evolved a defense system in their chemical constitution that fight against disease and infections from bacteria and fungi.

People have used these secondary metabolites in plants to serve many purposes over the course of time. Dyes (indigo), fragrances (essential oils), natural flavors (vanillin), insecticides (rotenone), poisons (strychnine), hallucinogens (morphine), stimulants (caffeine), and therapeutic agents (quinine) are some of the examples of secondary metabolites that humans have derived from plants (Wink, 2009). These defensive phytochemicals often contain medicinal activity that can lead to novel pharmacological discoveries to treat human maladies and disease (Inui, et al., 2012; Reichling, 2009).

Phenolic compounds are a class of secondary metabolites that are synthesized during the plant's development in response to threats from the environment like infections, wounding, and UV radiation (Stalikas, 2007). Plant polyphenols are a large and heterogeneous group of phytochemicals that have been named to have the potential for the prevention and management of type 2 diabetes (Lin, et al., 2016). These phytochemicals are found in many different fruits and vegetables in the human diet, including cranberries, raspberries, strawberries, apples, grapes, cucumbers, and onions. Polyphenols are a subject of study lately with research showing the ability of these compounds to inhibit the formation of advanced glycation end products, protect against β -cell degeneration, and inhibit digestive enzymes.

(Crascì, et al., 2018; Dall'Asta, et al., 2015; Lin, et al., 2016). Advanced glycation end products (AGEs), or glycotoxins, are made via a non-enzymatic reaction between reducing sugars (glucose or fructose) and proteins, lipids, or nucleic acids. AGEs contribute to the oxidant stress and inflammation that cause serious complications in the macro- and micro-vascular systems in type 2 diabetic patients (Stirban & Tschöpe, 2015).

Many botanical plants (including basil, bitter melon, fenugreek, ivy gourd, nopal, ginseng, cinnamon, psyllium, and garlic) contain active constituents that help control high blood glucose levels through several mechanisms of action (El-Beshbishy & Bahashwan, 2012; Lin, et al., 2016; Ota & Ulrih, 2017; Rodrigues Franco, et al., 2018). These mechanisms are reversing oxidation, the inhibition of digestive enzymes that break down carbohydrates and delay absorption into the bloodstream, the stimulation of insulin secretion, activation of insulin receptors and affecting glucose uptake in insulin-sensitive tissues (Ota & Ulrih, 2017). In this study, I sought to examine the capability of the root bark extract of *Oplopanax horridus* in acting as an anti-oxidant and inhibit digestive enzymes. This activity is through the activity of phytochemicals, powerful secondary metabolites found in the root bark of devil's-club.

4.3.3 Collection

Harvesting:

In the year 2000, seven Stimpson siblings donated 116 acres to Whatcom land trust to form the Stimpson Family Nature Reserve located in the Lake Whatcom watershed near Bellingham, Washington. The reserve is a beautiful middle-to-old growth forest draped in ferns and moss, with small wetlands, creeks, and ponds throughout that encourage the abundant

growth of a diverse variety of native plants, including *Oplopanax horridus*. In 2014, I obtained a permit from the Department of Natural Resources (Washington), to gather the root for scientific research purposes in this nature reserve. Devil's-club prefers low places in older forests, especially near streams and ponds and the Stimpson reserve was an ideal environment to identify and gather the specimens. In the winters of 2014 and 2015, I carefully gathered samples of the roots and rhizomes from various established areas of devil's-club in the reserve.

4.3.4 Exhaustive Extraction- Soxhlet Apparatus

Soxhlet extraction is a procedure for extracting organic compounds from solids that ensures a direct contact of the sample matrix with the sample solvent using continuous extraction. This method is typically used to isolate and concentrate non-polar, or water-insoluble, and polar, or water-soluble, organic compounds in preparation for chromatographic procedures. This extraction method is ideal as it uses inexpensive glassware, requires little manipulation once loaded, and is highly efficient as the solvent is recycled with a complete extraction of material due to the length of reflux (12-24 hours).

Assembly

The Soxhlet extractor has three main components: a percolator that circulates the solvent, a thimble (thick filter paper shaped like a long cup) that holds the sample to be extracted, and a siphon apparatus that empties the thimble when full. The thimble containing the sample is loaded into the main chamber of the Soxhlet extractor. The solvent used for extraction is poured into the distillation flask and then placed on the heating element with the Soxhlet extractor placed above it. Lastly, the reflux condenser is placed above the extractor.

Extraction

A solid sample is placed in the extraction thimble to be extracted using a series of solvents in the Soxhlet extractor. An organic solvent is heated to reflux. The vapors of the solvent travel up the distillation vessel and condense along the cool walls of the condenser. The condensed warm solvent fills the thimble containing the sample until the Soxhlet apparatus empties the solvent via a siphon back into the distillation flask. The extraction is usually left for hours and the material is extracted into the solvent in a process that is considered exhaustive, as it is repeated to extract like components into the solvent wholly. This form of extraction is desirable because it recycles the solvent and a small amount of the solvent is needed. After the extraction, the solvent is removed using rotary evaporation, and the extracted compounds are stored to be studied.

A crude extract can be fractionated in a mild manner that does not induce chemical change through serial exhaustive extraction (SEE) using the Soxhlet apparatus. This method allows the natural product chemist to take the primary step in the isolation of a medicinal active constituent without affecting the activity. The specimen of study is extracted using solvents that vary from non-polar, intermediate polarity to polar, thus producing fractions that carry active constituents ranging from lipophilic to hydrophilic.

4.3.5 Plant Hypoglycemic Drug Screening Methodology

The scientific investigation of traditional medicines has historically led to the discovery of new leads for antidiabetic medicines. This investigation requires a systematic approach using the plant samples in bioassays that may predict therapeutic efficacy. Bioassay-guided

antidiabetic drug discovery is divided into two classes: *in vivo* and an *in vitro*. *In vivo* techniques for studying hypoglycemic activity uses animals or diabetic humans as subjects of study. A common method is inducing hyperglycemia in rodents using alloxan or streptozotocin, pancreatic β -cell toxins, to mimic the dysfunction of insulin-producing β -cells in type II diabetics. Extracts of plant sample are then administered to the rodents and glucose levels are measured against a control. *In vivo* studies are necessary for the path of new drug development but should follow *in vitro* testing procedures before subjecting animals or human to experimentation. *In vitro* experiments are a valuable pre-screening method of drug discovery as they occur in a controlled laboratory setting, are relatively inexpensive, and do not require living organisms as subjects of study.

Tight control of postprandial plasma glucose in the early treatment of type 2 diabetes can halt the progression of the disease. Acarbose, a microbial product initially isolated from strains of *Actinoplanes* sp, is a current medication used to control postprandial hyperglycemia via inhibition of α -amylase and -glucosidase, the enzymes responsible for the breakdown of polysaccharides to monosaccharides (Marles & Farnsworth, 1995; Li, et al., 2016). The inhibition reduces the amount of glucose released from carbohydrates, thus causing a delay in the postprandial increase in glucose and triglycerides in the bloodstream. Research with acarbose identifies this inhibitor to improve the oxidative stress and inflammation in type 2 diabetic patients-allowing for a reduction in postprandial glucose levels and an improvement in diabetic complications. Yet, unwanted side effects like diarrhea and stomach cramps cause many patients to stop taking the medication.

4.3.6 Antioxidant Assays

Reactive oxygen species (ROS) can be produced during normal metabolism or can be induced by UV radiation and pollutants. The ingestion of foods rich in antioxidants can correct a disturbed antioxidant/pro-oxidant balance. Many disorders, like atherosclerosis, Alzheimer disease, arthritis, and cancer may be related to an increased concentration of free radicals in people's bodies (Stankovic, Niciforovic, Topuzovic, & Solujic, 2011). Phenols that occur naturally in plants and foods are beneficial to the human body with their ability to reverse oxidation, a reaction that leads to a plethora of problems in the body's systems. The phenolic group in polyphenols can accept an electron from free radicals within the body, forming a stable molecule that stops the destructive oxidation chain reaction in the body's cells. Thus, phenolic compounds protect cells against oxidative damage, limiting the risk of the many degenerative diseases (i.e., cancer, Alzheimer's, type 2 diabetes) associated with oxidative stress (Pandey & Rizvi, 2009).

The failure of β -cell sensitivity to glucose and the loss of first-phase and the decrease of second-phase of insulin secretion precipitates the development of type 2 diabetes as it results in chronic hyperglycemia (Makrilakis, 2006). Chronic hyperglycemia leads to excessive oxidative stress, caused by an increased number of intracellular reactive oxygen species (ROS), contributing to these metabolic abnormalities, the destruction of the pancreatic β -cells, and, ultimately, the acquisition of full-blown diabetes. β -cells have a low antioxidative capacity and are highly vulnerable to oxidative stress. Any protective action against this stress can prevent or delay the onset of type 2 diabetes. Physicians advise their t2dm patients to eat a diet high in fiber and low in processed complex carbohydrates. Foods like whole grains, berries, fruits, and

vegetables are good sources of fiber and rich in polyphenolic compounds. Studies show that polyphenols protect pancreatic β -cells against oxidative damage and improve the ability of these cells to secrete insulin and resist the stress that leads to diabetic complications (Dall'Asta, et al., 2015). The aim of this study was to determine the total phenolic content in plant extracts to determine antioxidant activity using the Folin-Ciocalteu total phenolics assay.

4.3.7 Folin-Ciocalteu Total Phenolics Assay

The Folin-Ciocalteu assay (often used to determine astringency, bitterness, and other character traits in wine) is a simple and widely-used method utilized to quantify phenolic substances in food and plants (Singleton, Orthofer, & Lamuela-Raventos, 1999; Singleton & Rossi, 1966; Waterhouse, 2002). Colorimetry based on a chemical reduction of the reagent, a mixture of tungsten and molybdenum oxides, determines the total phenolics in the sample of interest. The phosphomolybdic-phosphotungstic acid reagent is reduced by the antioxidative activity of phenols present in the sample to generate a blue-colored complex detected with a spectrophotometer (Stalikas, 2007). The intensity of the light absorption at 765nm is proportional to the concentration of phenols within the sample. At room temperature, the color develops slowly and heating the sample speeds up the process. Gallic acid is a secondary polyphenolic secondary metabolite that is a powerful antioxidant known to have cardioprotective, anti-hyperlipidemic, and anti-hyperglycemic activity (Zanwar, Badole, Shende, Hegde, & Bodhankar, 2014). In this experiment, gallic acid is used as the standard with the number of phenols present expressed as GAE (gallic acid equivalency), a concentration of milligrams per liter.

4.3.8 α -Glucosidase and α -Amylase Inhibition Assays

The digestion of starch evolves in stages. Digestion begins in the mouth where saliva partially breaks down the long-chain sugars due to the presence of the enzyme α -amylase. The hydrolysis of dietary polysaccharides, or complex carbohydrates like starch, greatly contributes to elevated blood glucose levels in modern humans. Digestive enzymes are crucial in the hydrolysis of these complex carbohydrates, those being named α -amylase originating in the pancreas and α -glucosidase found in the brush border cells of the upper small intestine. The inhibition of these enzymes will ultimately delay the digestion of these carbohydrates, prolonging digestion and reducing the rate of glucose absorption in type 2 diabetes mellitus patients (Dehghan, Salehi & Amiri, 2018). Reduction of blood glucose concentration also decreases insulin demand on the pancreas and increases insulin sensitivity in type 2 diabetic patients (Li, et al. 2016).

α -Glucosidase inhibitors (AGI) act competitively to block the α -glucosidases, enzymes responsible for the breaking down of long sugars (di-, oligo-, and polysaccharides) to single sugars (monosaccharides) in the first half of the small intestine. AGI delay the digestion of these complex carbohydrates resulting in slower absorption of glucose into the bloodstream. Acarbose, miglitol, and voglibose are three well-known AGI used as oral hypoglycemic agents as adjunctive therapy to assist diabetic patients in controlling low glycemic indices (Leroux-Steward, Rabasa-Lhoret & Chiasson, 2015). All three are poorly absorbed by the gastrointestinal tract and produce uncomfortable side effects are abdominal pain, gas production, and diarrhea.

Controlling postprandial hyperglycemia via inhibition of the glucosidase digestive enzymes decreases the diabetic patients' exposure to high glucose concentrations and reverse damaging effects of hyperglycemia. Studies show that postprandial glucose (PPG), the level of glucose within 1-2 hours of eating, is a potent mediator of microvascular and macrovascular complications in type 2 diabetics with increased levels of PPG leading to increased risk of cardiovascular events (Mannucci, Monami, Lamanna, & Adalsteinsson, 2012). A therapeutic approach to decrease postprandial hyperglycemia is to slow the absorption of glucose with medicine that inhibits digestive enzymes. The discovery of new medications with α -glucosidase inhibitory activity is a promising field of research in the quest for reducing morbidity and mortality in diabetic patients (Dehghana, 2018). The inhibition of the digestive enzymes that metabolize carbohydrates is an effective therapeutic approach for reducing postprandial hyperglycemia. In this study, digestive enzyme inhibition bioassays were conducted *in vitro* to ascertain if the extract of the inner root bark of *Oplopanax horridus* has antidiabetic activity.

Experimental

Many experiments in the fields of medicine, biochemistry, and biology will be performed three times, or in triplicate, and then take the average of the results or measurements as the response variable (Singer, Pedroso-de-Lima, Tanaka, & González-López, 2007) In this study, the extracts of devil's-club were tested in triplicate to quantify the phenolics, chemicals known for their antioxidant, anti-glycating capabilities and test for digestive enzyme inhibitory activity and, consequently, hypoglycemic activity.

Sample preparation and extraction of *Oplopanax horridus*

Plant material:

Samples of the roots and rhizomes of *Oplopanax horridus* were gathered from the Stimpson Family Nature Reserve in Bellingham, Washington. Permission was granted by the Department of Natural Resources to gather the root for scientific research purposes only.

Preparation of crude extracts and solvent partitioning of the crude extract:

Upon returning to the Vyvyan lab at Western Washington University, the roots and stalks were washed of mud and the outer layer was carefully scrubbed to remove thorns and rough bark. The inner bark of the roots and stalks were peeled away in 2-3" strips. After drying for 24-48 hours, the dried strips were ground to a fine powder that resembled nut flour and smelled of sweet dirt. In the first series of extractions, there were three types of root bark examined; the inner root bark (IRB) of the fallen stalks that rooted into rhizomes, the greenish inner root bark

(GRB) of the stalk, and the inner root bark of the “true root” (TRB) that grew from the rhizomes. In the second series of extractions, only the TRB root bark was gathered and prepared to be extracted.

Extraction of Devil’s-club:

The dried and powdered inner root bark of the root and rhizomes of *Oplonanax horridus* (devil’s-club) was subjected to exhaustive serial extraction using the Soxhlet apparatus. The extractions were carried out in five phases for 24 hours using the solvents: hexanes, dichloromethane, ethyl acetate, acetone, and methanol. The first extraction series consisted of 32.2 g of inner root bark of rhizome and stalk of *O. horridus*. The five non-polar to polar extracts yielded a spectrum of yellow to orange odorous liquids. Only the methanol extract contained dark brown resin-like solids that foamed upon evaporation in a rotary evaporator. The second extraction consisted of 32.7 g of true root bark which was subjected to the same series of nonpolar to polar solvents. This set of extracts yielded a similar smell and color as the first extraction. The third extraction consisted of 33.5 g of the dried greenish inner stalk and root bark. This series of extracts yielded a dark green extract in the hexanes, a dark brown/orange extract in dichloromethane, a bright yellow extract in the ethyl acetate, and a clear bright orange solution in the methanol. The acetone extraction yielded salts and precipitate that would not dissolve with polar solvents, including water and a scrub brush.

Final Extraction:

The final extraction of true root bark (34.8 g) took place in April of 2016. The inner root bark of *Oplonanax horridus* was collected in the winter of 2016 from Stimpson Family Reserve. The powdered inner root bark (34.8 g) was placed in the thimble to be serially extracted with the Soxhlet apparatus using the following solvents in sequence: hexanes, dichloromethane, ethyl acetate, acetone, and methanol. The solvent of each sub-fraction was evaporated at -40°C under vacuum using a rotary evaporator. The concentrated samples were then transferred to scintillation vials for storage.

Total phenolic content estimation using Folin-Ciocalteu Method

Chemicals and reagents:

Gallic acid, anhydrous sodium carbonate, Folin-Ciocalteu reagent (phosphomolybdate and phosphotungstate), dimethylsulfoxide (DMSO), α -glucosidase from *Saccharomyces cerevisiae*, 4-nitrophenyl β -D-glucopyranoside (pNPG), potassium sodium tartrate tetrahydrate, 3,5-dinitrosalicylic acid, phosphate buffer powder, α -amylase from *Aspergillus oryzae*, and maltose were obtained from Sigma-Aldrich.

Materials:

Gallic Acid

Anhydrous Sodium Carbonate

Folin-Ciocalteu Reagent (phosphomolybdate and phosphotungstate)

Dimethylsulfoxide (DMSO)

Preparation of materials:

Dried *O. horridus* root bark was gathered from the Stimpson Nature Reserve under the guise of the Department of Natural Resources, Washington.

In a 100-mL volumetric flask, dry gallic acid (0.5 g) was dissolved in ethanol (10 mL) and diluted to volume with water to make the gallic acid starch solution. Anhydrous sodium carbonate (200g) was dissolved in water (800mL) to make the sodium carbonate solution. The solution was brought to a boil, cooled, filtered, and stored in a 1L bottle.

Folin-Ciocalteu Method:

The total soluble phenolic compounds in the different extracts were determined with the Folin-Ciocalteu reagent using gallic acid as a standard. The samples were extracted into five solvents: hexanes, dichloromethane, ethyl acetate, acetone, and methanol. Samples were serially diluted to 50, 100, 150, 250, 500 $\mu\text{g}/\text{mL}$. Each calibration solution, sample, and blank (20 μL) was pipetted into a glass vial then mixed with DMSO (1.58mL) and Folin-Ciocalteu reagent (100 μL). After 30 s., NaHCO_3 (300 μL) solution was added to the reaction mixture. The reaction was stopped after 30 min. (40°C) and left on ice to cool. The reaction mixture was then transferred to cuvettes and the absorbance was measured at 765nm versus blank sample on a spectrophotometer (Jasco UV-Vis-NIR V-670).

Calibration Curve Preparation:

In a 100mL volumetric flask, 0, 1, 2, 3, 5, and 10 mL of gallic acid stock solution was diluted to volume with purified water. The solutions contained 0, 50, 100, 150, 250, and 500 $\mu\text{g}/\text{mL}$ of gallic acid, respectively.

Spectrometric Analysis:

Each calibration, sample, or blank solution (20 μL) was pipetted into separate cuvettes. Folin-Ciocalteu reagent (100 μL) was then added to each cuvette. After 30 seconds, the sodium carbonate solution (300 μL) was added. The solutions were warmed in a water bath (40°C) for 30 minutes. The absorbance of each solution was read (765nm) against the blank. Gallic acid

was used to design a calibration curve and results are expressed in gallic acid equivalents (mgGAE/g dry extract). The sample concentration was calculated from the gallic acid (50-500 $\mu\text{g}/\text{mL}$) standard curve equation and the results were expressed as mg gallic acid equivalent per gram of dried weight sample (mg GAE/g d.w.) The total phenolic contents of the extracts were calculated using Eq. (1). Dimethyl sulfoxide was used as the blank. The analyses were done in triplicate.

$$TPC = c * V / m \quad (1)$$

Where c is the concentration of the sample from the calibration curve (mg/mL), V is the volume (mL) of the solvent used for the extraction, and m is the weight (g) of the dried sample used.

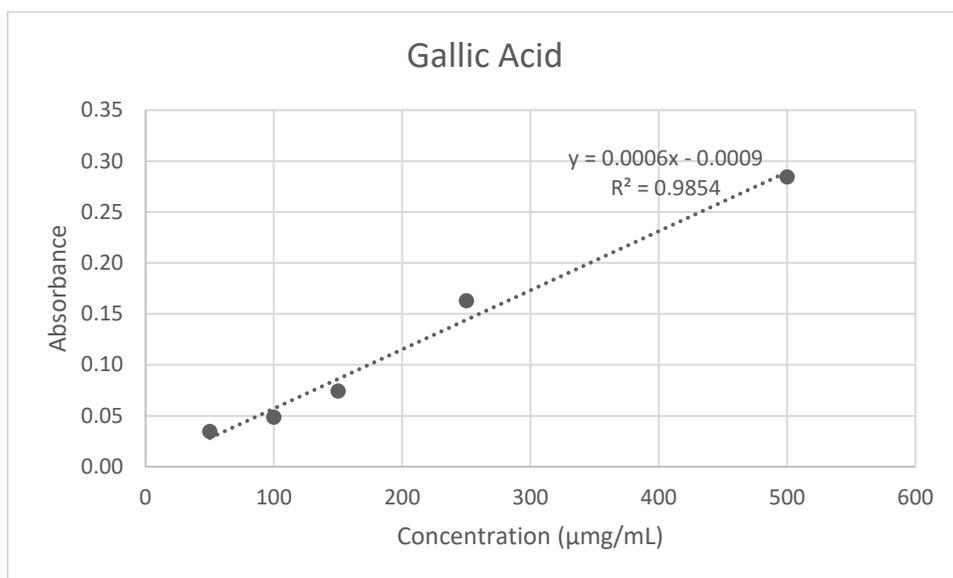


Figure 10: Gallic acid calibration curve. This curve represents a standard in phenol quantification, gallic acid. The slope equation of the gallic acid, $y = .0006x - .0009$, was used in this case to quantify the number of phenols in the devil's-club extracts.

Determination of the α -glucosidase inhibitory activity of crude extract fractions

In this study, extracts of *Oplopanax horridus* of varying concentrations were tested against α -glucosidase to observe the inhibitory activity.

Materials:

α -glucosidase from *Saccharomyces cerevisiae*.

Phosphate buffer (pH 6.9)

Anhydrous sodium carbonate

4-Nitrophenyl β -D-glucopyranoside (pNPG)

Method

This enzymatic inhibitory assay was carried out using a modified method described by Kazeem et al. in which 4-Nitrophenyl β -D-glucopyranoside (pNPG) as the substrate (2013).

Figure 10 The substrate solution (pNPG) was prepared in 20mM phosphate buffer (pH 6.9). α -Glucosidase (100 μ L; 1.0U/mL) was pre-incubated (20°C) for 3-5 minutes with extracts (50 μ L) of varying concentrations (5mg/mL-.078mg/mL) in test tubes. pNPG solution (50 μ L.; 3.0mM) was added to the extracts and placed in a warm bath oven for 20 minutes at 37°C. The reaction was stopped by adding Na₂CO₃ (2.0 mL; 0.1M). The inhibitory activity of each extract was determined by measuring the concentration of the yellow-colored paranitrophenol released from pNPG on the 96-well plate reader at 405nm (Kazeem, Adamson & Ogunwande 2013).

Figure 11 The reaction system without root bark extracts was used as a control.

Materials:

α -amylase

Anhydrous sodium carbonate

Sodium potassium tartrate

3,5-Dinitrosalicylic acid

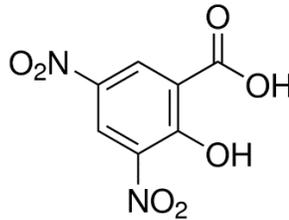
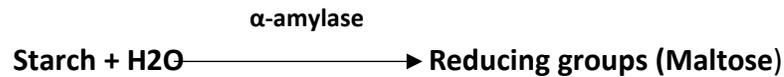


Figure 12: 3,5-Dinitrosalicylic acid

The objective of this experiment was to standardize a procedure for determining the enzymatic activity of α -amylase and test sample extracts *in vitro* to measure inhibitory activity.

One unit of α -amylase will liberate 1.0 mg of maltose from starch in three minutes at pH 6.9.



Procedure conditions:

Temp. 20°C

pH 6.9

A_{540nm}

Lightpath-1cm

Method

A total of 250 μL (0.625-10mg/mL) of extract and 250 μL of 0.02M sodium phosphate (pH 6.9) buffer containing α -amylase (1.0U/mL) were mixed in test tubes. A control was also prepared

with the α -amylase solution in which extract was replaced with distilled water (250 μ L). The solutions, sample extracts, blank, and control, were incubated for 5 minutes at room temperature (20°C). The starch solution (250 μ L) was then added to the reaction mixture and further incubated for 3 minutes. The reaction was terminated by adding 3,5-Dinitro salicylic acid (250 μ L) to the mixtures. The test tubes were placed in boiling water for 15 minutes, then set on ice to cool. Reaction mixture (containing α -amylase (1.0U/mL), starch solution, and devil's-club extracts) was diluted with 2.25 mL of purified water to a total volume of 3 mL. The control, blank, and extract samples absorbances were measured at 540nm. The results were calculated using the equation (2):

$$(2) \quad \% \text{ Inhibition} = \frac{\text{Abs}_{\text{control}} - \text{Abs}_{\text{extract}}}{\text{Abs}_{\text{control}}} \times 100$$

Data analysis

This experiment was performed in triplicate and the data was expressed as mean +/- standard deviation (σ or SD).

Results and Discussion

In this study, I evaluated the antioxidant capacity and the *in vitro* inhibitory activities against α -amylase and α -glucosidase within extracts (hexanes, dichloromethane, ethyl acetate, acetone, methanol) of the root bark of *Oplopanax horridus*. Each experiment was conducted in triplicate with the results equilibrated by using the standard mean of the three. I ran the tests three times in replicate, using the same concentrations, samples, and blanks, in order to calculate statistical error and deviation using standard deviation. My main findings indicate that the extracts exhibit enzyme inhibitory activity against α -glucosidase and α -amylase. Findings from the total phenolics capacity assay show that the ethyl acetate, acetone, and methanol extracts contain antioxidizing polyphenols, with the methanol extract containing the greatest number. The root bark contains antioxidant activity, leading to its capability to slow down the acquisition of diabetic complications and the severity of the disease. The root bark may show anti-hyperglycemic activity, in that it inhibits the enzymes responsible for the breakdown of long sugars.

Antioxidant capacity of root bark extracts in relation to phenolics

The results of the total phenolic contents of the five different extracts from the true, green, and inner root barks of *Oplopanax horridus* obtained from ethyl acetate, acetone, and methanol solvents are shown in **Table 3**. The total phenolic contents of the true root bark extracts (ethyl acetate, acetone, and methanol), expressed as gallic acid equivalents (GAE) per gram of dry extract, were found to be 1.64, 2.39, 6.55 mg/g GAE respectively. Among the analyzed extracts, the true root bark extracted with methanol had the highest concentration of

phenolics (6.55 mg/g GAE). **Table 3** Green root bark extracted with acetone had the highest concentration of phenolics (3.14 mg/g GAE) when compared to the true and inner root barks (2.39 mg/g GAE; 2.13 mg/g GAE) extracted with acetone. **Figure 10** shows a clear depiction of the significant difference between the concentrations of phenolics in the extracts obtained using selected solvents (ethyl acetate, acetone, methanol and unique root barks (green root bark- GRB, inner root bark- IRB, and true root bark-TRB)).

Table 3: Total phenolics of *O. horridus* expressed in Gallic Acid Equivalency (GAE). Total phenolics of five selected root bark extracts (GRBACE-green root bark acetone, IRBACE- inner root bark acetone, TRBEA- true root bark ethyl acetate, TRBACE- true root bark acetone, TRBMET-true root bark methanol) using the Folin-Ciocalteu method were derived from concentrations ranging from 50mg/mL-500mg/mL as expressed in mg/g GAE.

	50mg/mL	100mg/mL	150mg/mL	250mg/mL	500mg/mL
Extracts	Gallic Acid Equivalents mg/g				
GRBACE	0.795	1.1	1.12	1.97	3.14
IRBACE	0.71	0.81	1.285	1.81	2.13
TRBEA	0.392	0.469	0.639	0.953	1.64
TRBACE	0.665	0.864	0.964	1.33	2.39
TRBMET	0.92	1.91	2.68	3.73	6.55

Plants and foods high in phenolic compounds are known to hold antioxidant activity, a beneficial attribute for those with type 2 diabetes as the disease leads to oxidative stress within cellular processes. Phenolic compounds found in secondary metabolites are known to scavenge free radicals and reduce non-enzymatic glycation (Franco, et al., 2017). The objective of this study was to examine the distribution of phenolic compounds in different extracts of the green, inner, and true root barks of *Oplopanax horridus*. The polar extracts proved to be effective in the extraction of phenolic compounds. In relation to the solvents used, moderate concentrations of phenolic compounds were found in the ethyl acetate, acetone, and methanol extracts, with the highest amount found in the highly polar methanol extract.

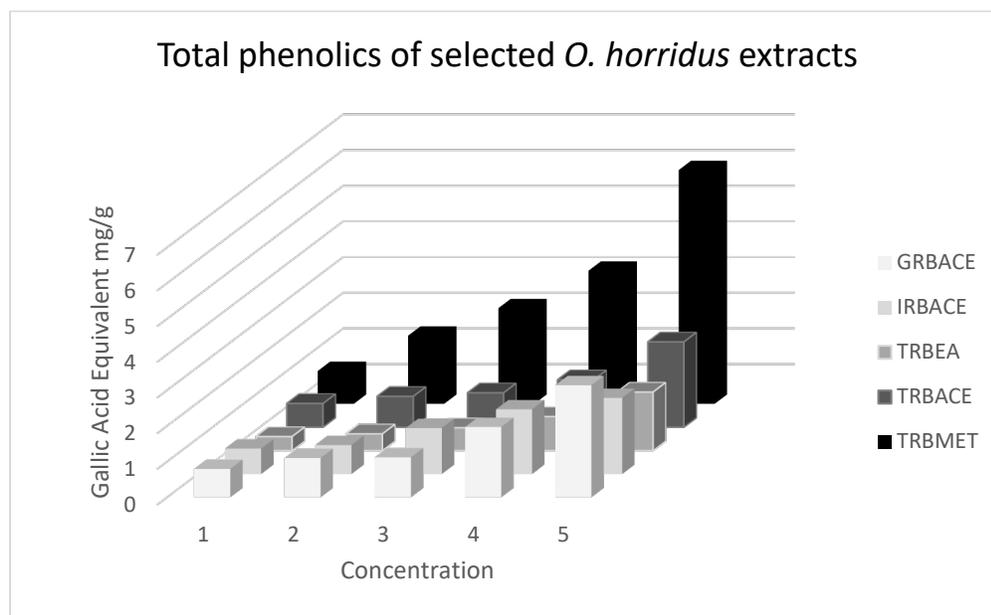


Figure 13 Total phenolics of five selected root bark extracts of *Oplopanax horridus*. The total phenolics of five root bark extracts (green root bark acetone-GRBACE, inner root bark acetone-IRBACE, true root bark ethyl acetate-TRBEA, true root bark acetone-TRBACE, true root bark methanol-TRBMET) was quantified using the Folin-Ciocalteu method.

Enzymatic inhibition

α -Glucosidase inhibitory activity of crude extract fractions

In this study, the inner root bark extracts of *O. horridus* were evaluated to determine the inhibitory activity of digestive enzymes. Figure 12 shows the percentage inhibition of α -glucosidase by the five extracts of *O. horridus*. The samples extracted with acetone and methanol exhibited negative inhibition at lower concentrations. Methanol extracts displayed marked negative inhibition in concentrations ranging from .157-2.5 mg/mL. The acetone extract showed the highest inhibition at 1.25 mg/mL with decreasing activity as the concentration increased. Percent inhibition of α -glucosidase with the methanol extract was highest at 5mg/mL. It is important to note that acetone and methanol extracts showed a high standard

error. The hexanes, dichloromethane, and ethyl acetate extracts showed high inhibitory rates through the dilution series with a low standard error. **Table 3 Figure 12**

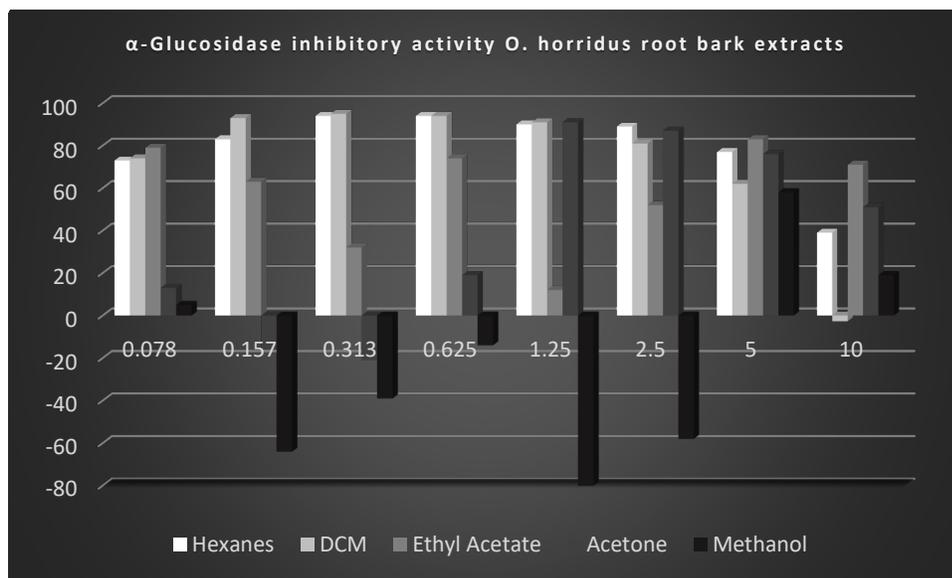


Figure 14: *O. horridus* root bark extracts inhibition of α -glucosidase *in vitro*: the hexanes, dichloromethane, and acetone extracts show inhibition of the digestive enzyme at lower concentrations. All extracts show inhibition at 5mg/mL.

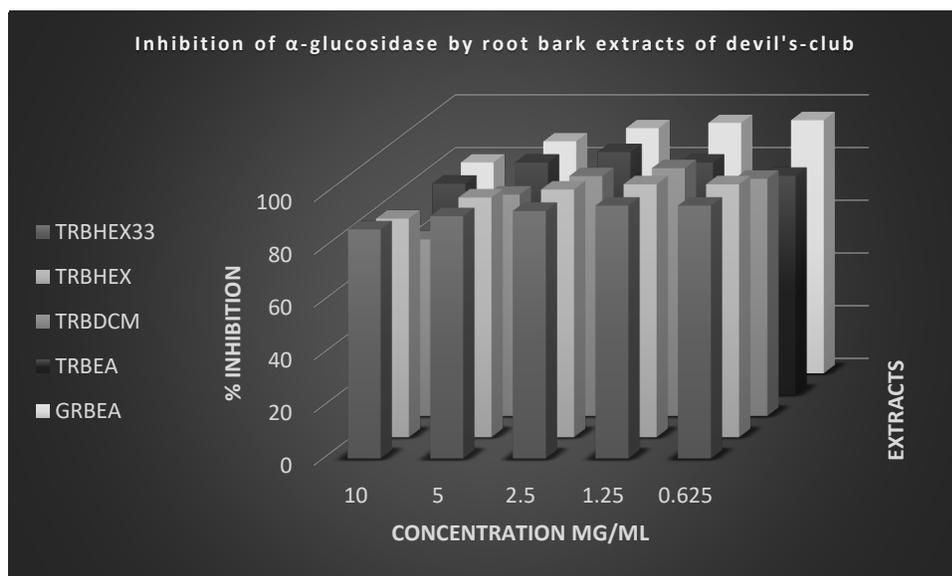


Figure 15: Percent inhibition of α -glucosidase by green root bark (GRB) and true root bark (TRB) extracts of *Oplopanax horridus*. α -Glucosidase was tested against hexanes, dichloromethane (DCM), and ethyl acetate extracts of *O. horridus* with concentrations ranging from 10-0.625 mg/mL to assess inhibitory activity using the colorimetric method.

Table 4: Effect of *Oplopanax horridus* on α -glucosidase inhibition activity by colorimetric method and release of pNPG in percent inhibition with standard deviation (σ). The true root bark hexanes, dichloromethane, and ethyl acetate extracts recorded high inhibitory activity with a low standard deviation. Extracts are listed as followed: TRBHEX33 (true root bark hexanes extract-first extraction), TRBHEX (true root bark hexanes extract final extraction), TRBDCM (true root bark dichloromethane-final extraction), TRBEA (true root bark ethyl acetate final extraction), GRBEA (green root bark ethyl acetate-first extraction).

Concentration:(mg/mL)	10	5	2.5	1.25	0.625
Extracts					
TRBHEX33	87	92	94	96	96
σ	0.74	0.57	1.2	0.32	0.35
TRBHEX	83	91	94	96	96
σ	3.1	1.2	0.25	0.23	0.15
TRBDCM	67	84	91	94	90
σ	2.9	2	0.45	0.21	5
TRBEA	80	88	92	88	83
σ	1.2	0.4	0.06	6.4	6.6
GRBEA	80	88	93	95	96
σ	1.1	0.35	0.23	0.23	0.21

α -Amylase inhibitory activity of crude extract fractions

The objective of this experiment was to measure the inhibitory activity of *O. horridus* extracts *in vitro* against α -amylase. The root bark extracted with dichloromethane did not inhibit the enzyme. All other extracts (excepting the dichloromethane fraction) showed inhibitory activity on the enzyme. The root bark extracted with methanol, ethyl acetate, and hexanes inhibited the enzyme ranging from 9.3% to 19.4%. The acetone extract of *Oplopanax horridus* showed 35% inhibition of the α -amylase enzyme *in vitro*. **Table 5**

Table 5: Percent inhibition of α -amylase when tested with *O. horridus* extracts with standard deviation (σ).

Hexanes	Dichloromethane	Ethyl Acetate	Acetone	Methanol
12.8%	-17.2%	19.4%	35%	9.3%
σ 2.7	σ .07	σ 2.4	σ 2.5	σ 2.5

Effect of root bark extracts on α -amylase and α -glucosidase activities

Strict glycemic control in patients with type 2 diabetes reduces the risk of developing micro- and macrovascular complications and improves health outcomes of those with the disease (Shaefer & Anderson, 2016). Postprandial hyperglycemia contributes to most of the exposure to high blood sugar in the diabetic condition, necessitating patients to control their levels of hyperglycemia soon after eating. Controlling glucose levels in the blood requires lifestyle modifications and an intense regiment of antidiabetic drugs and health interventions. Glucosidase and α -amylase inhibitors delay digestion of complex carbohydrates, thus slowing the dump of glucose into the bloodstream. The list of medicines prescribed to control postprandial hyperglycemia is short, and new medicines offer diabetic patients additional means to control blood sugar levels.

The antidiabetic activity of root bark extracts from *Oplopanax horridus* was evaluated by measuring the percent inhibition of the extracts upon the α -amylase and α -glucosidase digestive enzymes. The bioassays were distinguished by different extracts that were separated using a non-polar to polar solvent system to separate active constituents into crude fractions according to hydrophilicity and lipophilicity. Preliminary *in vitro* tests reveal inhibition against both α -amylase and α -glucosidase digestive enzymes. In this study, the hexanes, dichloromethane, and ethyl acetate extracts showed high inhibitory activity against the α -glucosidase enzyme (see **Table 4**). The acetone extract showed marked inhibitory activity against the α -amylase enzyme. As shown in **Figure 12** and **Figure 13**, all extract fractions (hexanes, dichloromethane, ethyl acetate, acetone, methanol) tested in this post-prandial hyperglycemia model showed efficacy in the inhibition of the enzyme α -glucosidase *in vitro*.

Post-prandial hyperglycemia will cause the development of microvascular complications and lead to glucose toxicity, a state that damages the insulin-producing β -cells in the pancreas. The inhibition of digestive enzymes slows down the break-down of complex carbohydrates, modifying the rise of blood glucose after eating. The activity of devil's-club root bark in inhibiting these digestive enzymes validates the long-time usage of this plant by the Indigenous Peoples of the Northwest Coast and may contain an active constituent that pharmacologically treats diabetic complications.

Conclusion

Two-Eyed Seeing refers to learning to see from one eye with the strengths of (or best in) Indigenous knowledges and ways of knowing, and learning to see from the other eye with the strengths of (or best in) Western knowledges and ways of knowing. . . and, most importantly, using both of these eyes for the benefit of all. Two-Eyed Seeing adamantly, respectfully, and passionately asks that we bring together our different ways of knowing to motivate people, Aboriginal and non-Aboriginal alike, to use all our understandings so we can leave the world a better place and not compromise the opportunities for our youth (in the sense of Seven Generations) through our own inaction. Albert Marshall, Mi'kmaw (Marshall, Marshall, & Bartlett, 2015, p. 16)

The Indigenous Peoples of the Pacific Northwest, including the Coast Salish and the First Nations sharing the border of British Columbia and Washington state, have a substantial repertory of healing foods, plants, and traditions that have been tested through Indigenous scientific methods and biomedical science to support health and prevent chronic diseases like type 2 diabetes (Körn and Ryser, 2009). Type 2 diabetes is a disease brought from the “outside”, centered around the loss of traditional foods and the loss of territory in which these great foods were gathered through careful cultivating practices. The high prevalence of diabetes within the Indigenous populations is a well-known fact, an accepted occurrence with the caveat that American Indians and Alaska Natives are predisposed to the disease. American Indians/Alaska Natives (AI/AN) are 2.3 times more likely to have a diagnosis of diabetes when compared to whites, AI/AN with diabetes are hospitalized more, take more trips to the ER, and are three to four times more likely to die from the disease (Duwe 2016). The focus of many research trials is the high prevalence of diabetes in Indigenous populations, looking to research their bodies and minds to discover why the disparity. Little focus is placed in the positive aspects of Indigenous approaches to healing and in the sanctifying of culture as the way to health. Successful interventions for diabetes in Indigenous Peoples are “taking control and

using community power, restoring traditional foodways and planting healing gardens, and playing or enjoying leisure time” (Duwe 2016, p. 624).

Diabetes treatment care programs that incorporate traditional ways of knowing, foods and medicine revitalization benefit Indigenous patients with type 2 diabetes. Scientific advances in public health, medicine, and nursing have contributed to the prevention and treatment of chronic diseases, improving the health and longevity of people on a global scale. Yet social determinants of health along with the legacy of colonization has created a health system of inequities and gaps in health between Indigenous and non-Indigenous populations (Marmot, 2005). Many medicines given to Indigenous diabetic patients treat the symptoms of diabetes but lack the depth of meaning to connect the patient to the medicine in a culturally meaningful way. Western health research can reveal medicinal activity and the mechanism of action, as shown in the research I conducted regarding the bioactivity of the root bark of *Oplopanax horridus*. However, research stemming from the Western scientific method alone is not adequate in the treatment of type 2 diabetes among Indigenous populations. What is needed is a health model designed within a paradigm of Two-eyed Seeing-- the harmonious collaboration of both Western Science and Indigenous Ways of Knowing.

Health care programs centered around a harmonious treatment program that incorporates Indigenous ways of knowing with the benefits of Western medicine offer Indigenous patients a positive pathway to health and self-management of type 2 diabetes. The knowledge of devil’s-club shares many of the epistemological characteristics of Indigenous science as referenced earlier in the description of the multi-contextual system of Indigenous Knowledge Systems by Cajete. Devil’s-club plays a pivotal role in many oral traditions, has been

observed and used to treat chronic diseases from generation to generation, and persists to the present day as a cultural keystone species. Physicians with greater knowledge and understanding of a deeply significant plant like devil's- club will connect with their patients and help them to nurture willingness for self-care and management beyond a strict Western medical regimen.

In 1938, Dr. Brockelsby and Dr. Large published a study which stated that there was a hypoglycemic substance in extracts derived from devil's-club. This study was followed by several other research trials to the present date with no solid evidence of the extract containing such a substance. Regular use of the tea previously recorded in ethnobotanical literature was reported to alleviate the symptoms of type 2 diabetes. These scientists were inspired to study the plant for anti-diabetic activity because of personal interactions with Indigenous patients who used the root bark tea to treat symptoms of diabetes and from reading ethnobotanical literature that wrote of the Indigenous use of the plant in the treatment of disease. The root bark extract of devil's-club has been used to treat chronic and contagious diseases in the Pacific Northwest for millennia with its most contemporary use being in the treatment of the symptoms of diabetes. Leslie M. Johnson describes a hypothesis that the more people that use the same plant across a broad range of distance and time along with its application across fields of spiritual and medicinal use and pharmacology confirm its medicinal value (2006). As told earlier, the range of devil's-club use is represented by over 38 linguistic groups in the region with thirteen groups recording ingestion of the root bark tea to treat diabetes (Lantz, Turner & Swerhun, 2004). Yet, scientific studies historically record the absence of hypoglycemic activity

in controlled fasting glucose tests, proving traditional use in treating diabetic symptoms as purely anecdotal.

The results from the bioassays that I conducted show that extracts of inner root bark of *Oplopanax horridus* contain antioxidative capability and inhibit the activity of pancreatic and intestinal digestive enzymes, α -amylase and α -glucosidase; an action which slows down the rise of glucose levels after eating a carbohydrate-rich meal. This study is the first report of the inhibitory activity of *Oplopanax horridus* root bark extract against α -amylase and α -glucosidase. These findings suggest that the root bark contains bioactive compounds that can be considered for future research in diabetic medicines. When I first designed this research project, I aimed to separate the five fractions into individual compounds using column chromatography. I then planned to test these possible bioactive compounds for their ability to reverse hyperglycemia and protein glycation, a biochemical reaction known to cause the macro- and micro-vascular hardening of cellular walls in the cardiovascular system. Future research can consist of this separatory method followed by testing individual compounds for the inhibitory activity to pinpoint if the activity is the result of one compound or a synergistic effect of a group of compounds. In finding that the crude extracts exhibit strong inhibition, research scientists can use this knowledge to continue looking into bioactivity within the root bark that may suggest a stronger medicine to treat post-prandial hyperglycemia. My desire is that this research would be conducted by Indigenous research scientists from the Pacific Northwest in which results and future medicinal findings would be considered protected by the laws of intellectual property rights.

Devil's-club persists as a vital medicine with a deeply embedded cultural identity, and it is in this identity that the continuity of Indigenous Knowledge systems endures helping to treat the disease. The memory of devil's-club lives through Indigenous oral traditions, marking stories and events of the past millennia to the present day in which records tell of the sacredness and medicinal activities of the plant throughout the Pacific Northwest. Devil's-club and the Indigenous Peoples of the Pacific Northwest share an enduring relationship in which the plant serves as an advocate in the health and well-being of Indigenous communities through cultural and medicinal pathways. Root bark extracts of *Oplopanax horridus* contain polyphenols that reduce the inflammatory response and are potent inhibitors of the digestive enzymes responsible for the breakdown of complex carbohydrates. These activities can regulate post-prandial glucose levels allowing for a gradual release of glucose into the bloodstream after eating a starch-rich diet and protect against oxidative pathways leading to diabetic complications. The results from the three bioassays in this research project support the use of devil's-club tea made from the root bark of the plant by the Indigenous Peoples of the Northwest Coast in the treatment of diabetes. Devil's-club as a medicine, with its deeply embedded cultural, spiritual, and medicinal background, can be a source of healing for type 2 diabetes.

“She explained how the plants gave her strength and healed her. At the villagers were wary, but they trusted the Girl, and chewed on the inner bark.

Once they rid the illness from the village, the people learned to respect the powerful plant.

These plants grown from the shredded bits of the giant's club are what we now call *S'axt*, Devil's club. Since the giant had fought many shaman, his club had absorbed their healing abilities. To this day, Devil's club, like a shaman, helps heal and protect us.”

How Devil's Club Came to Be by Miranda Kaagwéil Goade

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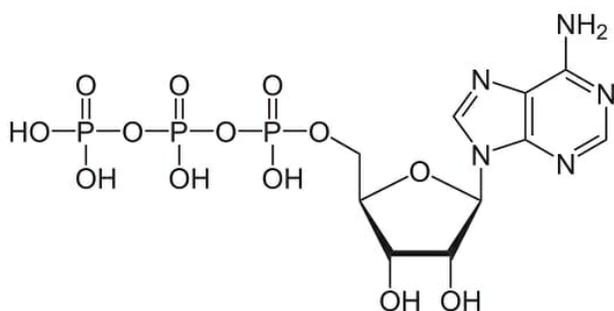
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Appendix

A. Glossary

adenosine triphosphate/ATP

the energy or fuel molecule used by the cells of the human body to perform work of any kind



Adenosine triphosphate- ATP

antioxidant

A molecule that inhibits the oxidation of other molecules.

α -amylase

An enzyme (glycoside hydrolase enzyme) that breaks down alpha bonds of large, alpha-linked polysaccharides like starch and glycogen into glucose and maltose. Amylase is found in human saliva and pancreatic juice. Pancreatic α -amylase cleaves $\alpha(1\rightarrow4)$ bound glucose molecules known as amylose.

Amylase catalyzes the breakdown of starch into simple sugars. It is produced in the salivary glands and in the pancreas.

α -amylase inhibitors

An oral agent that inhibits the action of α -amylase by forming a tight complex with amylase, inactivating the enzyme and causing a reduction in starch digestion.

α -glucosidase

An enzyme (glycoside hydrolase enzyme) that breaks down complex carbohydrates like starch and glycogen into their monomers. Alpha-glucosidase is located in the brush border of the small intestine and acts upon $\alpha(1\rightarrow4)$ bonds in starch and disaccharides, breaking them down to glucose. Alpha-glucosidase hydrolyzes terminal non-reducing $(1\rightarrow4)$ -linked alpha-glucose residues to release a single alpha-glucose molecule via a nucleophilic displacement or an oxocarbenium ion intermediate.

α -glucosidase inhibitors

An oral agent that delays the absorption of glucose in the small intestine and causes a reduction in the postprandial rise of glucose in the blood. These inhibitors selectively inhibit glucosidase enzymes in the brush border of the small intestine resulting in slower digestion and absorption of carbohydrates.

bark

The portion of the external woody stem or root that is found outside the cambium ring of a tree or shrub. Texture, thickness, and color vary between species, and with the age of each distinct plant.

cambium

A single layer of actively dividing cells responsible for the secondary growth of stems and roots in plants.

C-peptide

The connecting peptide (C-peptide) that joins insulin's A-chain to the B-chain in the proinsulin molecule. In the synthesis of insulin, preproinsulin is translocated into the ER (endoplasmic reticulum) of β -cells of the pancreas and is made up of an A-chain, a C-peptide, a B-chain and a signal sequence. After being cleaved by a signal peptidase, the peptide (proinsulin) is packaged into vesicles in the Golgi apparatus where the C-peptide is removed. After the cleavage of C-peptide, the insulin molecule remains bound by disulfide bonds.

empirical

based or derived from observation and/or experience

ethnobotany

The study of interactions and relationships between plants and people over time and space; including the uses, knowledge, beliefs, management systems, classification systems and language that contemporary and traditional cultures have for plants and the terrestrial and aquatic ecosystems in which they live. (Anonymous, 2007)

exocytosis

the movement of macromolecules (i.e. proteins, polysaccharides, hormones) from inside of a cell to outside of a cell

free radical

Molecules or molecular fragments containing one or more unpaired electrons in atomic or molecular orbitals. These unpaired electrons give a degree of reactivity to the free radical.

glucose

a sugar or monosaccharide with the molecular formula $C_6H_{12}O_6$ that is the end-product of carbohydrate digestion

glucagon

protein hormone produced by the alpha cells of the pancreas that stimulates the breakdown of glycogen in the liver into glucose

glycogen

a polysaccharide molecule with the molecular formula $C_6H_{12}O_5$ that is formed by and stored in the liver to be broken down by the pancreatic hormone glucagon into glucose

hydrophilicity**“water-loving”**

the principal state of affinity for water; readily dissolved or absorbed in water

hyperglycemia

The condition of having high levels of glucose in the blood.

A normal fasting glucose level is between 70-99mg/dL (3.9-5.5 mmol/L). Prediabetes is defined by an impaired fasting glucose of levels between 100-125 mg/dL (5.6-6.9 mmol/L). Diabetes is indicated by one or more testing results greater than 126 mg/d: (7.0 mmol/L).

In the 2-Hour Oral Glucose Tolerance Test (OGTT), a glucose level less than 140 mg/dL (7.8 mmol/L) is considered normal. A glucose level between 140-199 mg/dL is considered prediabetes or impaired glucose tolerance. A non-fasting glucose level that is equal to or greater than 200mg/dL (11.1 mmol/L) is an indicator of diabetes.

hypoglycemia

A condition characterized by a drop in blood glucose to a low level based on normal.

Symptoms of hypoglycemia include shakiness, anxiety, and nervousness. Also, a hypoglycemic event may present with altered mental status, tachycardia, palpitations, sweating, pallor, dilated pupils, nausea, vomiting, and headaches.

homeostasis

a state of equilibrium in the body

Indigenous

Naqshbandi et. al define the term Indigenous to be descendants from groups who were present in a region before the arrival of colonizers, who are self-identified and identified by other to a distinct cultural group forming a non-dominant sector of society, who maintain a cultural and social identity with at times a distinct language, and lastly, who have historical continuity and a unique attachment to traditional habitats, lifestyles and ancestral territories. (Naqshbandi, Harris, Elser, & Antwi-Nsiah, 2008)

Indigenous communities, Peoples and nations are those which, having a historical continuity with pre-invasion and pre-colonial societies that developed on their territories, consider themselves distinct from other sectors of the societies now prevailing in those territories, or parts of them. They form at present non-dominant sectors of society and are determined to preserve, develop, and transmit to future

generations their ancestral territories, and their ethnic identity, as the basis of their continued existence as Peoples, in accordance with their own cultural patterns, social institutions, and legal systems.

United Nations, Workshop on data collection and disaggregation for Indigenous peoples: the concept of Indigenous peoples, PFII/2004/WS.1/3 (2004) 1–4.

inflorescence

A flower cluster; manner of flowering.

insulin- *insula* (Latin) island

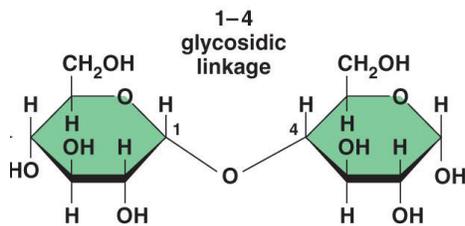
A peptide hormone produced by the beta cells of the pancreas that regulates the metabolism of fats, protein, and carbohydrates by promoting the absorption of glucose from the blood. Fat, liver and skeletal muscle cells absorb glucose that is then converted into glycogen (glyconeogenesis) or fats (triglycerides via lipogenesis).

lipophilicity

“fat-loving”

the principle state of solubility in fats or lipids

maltose



Maltose

Reducing disaccharide.

palmete

Leaf with veins that radiate from a central point, like spread out fingers pointing away from the palm.

pancreatic juice

A clear alkaline secretion of the pancreas that contains enzymes that aid in the digestion of carbohydrates, proteins, and fats.

panicle

A compound raceme; flowers are borne on branches of the main axis or on further branches.

petiole

The stem or stalk of a leaf.

phytochemicals

Plant secondary metabolites that are produced by plants for many functions; including UV protection, pigmentation to improve chances of pollination, improving plant's health and ability to survive, protection against herbivores and pathogens. These secondary metabolites are not involved in central function like reproduction and growth.

post-prandial hyperglycemia

After meal high blood sugar.

Blood sugar that's higher than 180 mg/dL two hours after eating is considered post-prandial hyperglycemia.

purgative

A substance or medicine that evacuates the bowels; purges; laxative.

raceme

An indeterminate inflorescence where the main axis produces a series of flowers on lateral stalks, with the oldest at the base and the youngest at the top.

reactive oxygen species (ROS)

chemically reactive chemical species

Formed as a natural byproduct of the normal metabolism of oxygen and assist in cell signaling and homeostasis. ROS can be formed while under environmental stress such as UV or heat exposure. ROS can damage DNA or RNA, oxidize amino acids in proteins, cause a variety of inflammatory responses such as cardiovascular disease. ROS are constantly being made and are required to drive regulatory pathways. Cells control ROS levels by balancing the generation of ROS with the elimination by a scavenging system. Under oxidative stress conditions, excessive ROS damages cellular proteins, lipids, and DNA.

sugar

A simple carbohydrate $(CH_2O)_n$ that contains three or more carbon atoms; one of which has a carbonyl group and the other hydroxyl groups.

Traditional medicine (TM)

The sum total of the knowledge, skill, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness. (World Health Organization 2000)

umbel

An inflorescence in which all the individual flowers are clustered at the top, are equal length and are arranged in a raceme.

B. Chemical constituents and research studies of bioactivity of *O. horridus*

2002 Bioactive Constituents of Alaskan Devil's Root (*Oplopanax horridus*, Araliaceae). *Economic Botany*, 56(3): pp. 285-287

Bloxton, James D. and Ara Der Marderosian

Four sesquiterpenes previously identified, α -cubebene, trans-nerolidol, spathulenol, oplopanone. Trans-nerolidol was identified as a major constituent in the root. Other compounds isolated and previously identified are stearic acid, stigmasterol, and β -sitosterol. (Bloxton & Marderosian, 2002)

1. A mixture of cis and trans nerolidol was shown to act as an inhibitory agent against neoplasia induced by azoxymethane in the large bowel in male rats. The rats were fed a diet of cis and trans nerolidol. (Wattenberg 1991)
2. Nerolidol was found to be a sedative and spasmolytic in mice.
3. Oplopanone acts as an antipyretic and antitussive.
4. Stigmasterol and β -sitosterol have been shown to contain antirheumatic and anticholesteremic properties. (Budaveri 1989)

2014 Chemical Constituents of the Plants from the Genus *Oplopanax* (Review). *Chemistry and Biodiversity*. 11():181-195

Huang, Wei-Hua; Zhang, Qing-We; Yuan, Chun-Su; Wang, Chong-Zhi; Li, Shao-Ping and Zhou, and Hong-Hao Zhou.

- A. Triterpenoids
- B. Sesquiterpenes
- C. Monoterpenoids
- D. Polyynes
- E. Phenylpropanoids
- F. Lignans
- G. Anthraquinones
- H. Flavonoids
- I. Fatty Acids
- J. Steroids
- K. Steroid glycosides
- L. Sugars

Effects of *Oplopanax horridus* on Human Colorectal Cancer Cells Li et al. 2010

(Li, et al., 2010)

Ethnopharmacological screening is a pathway of understanding how the medicinal knowledge of plants known by Indigenous caregivers provides new medicines based on biologically active natural products. The purpose of this study was to ascertain if devil's-club extract affects the growth of colorectal cancer cell lines and the mechanism behind its actions. Previous studies show that *Oplopanax horridus* possesses antiproliferative activity on several human cancer lines; i.e. breast cancer, leukemia, and ovarian cancer. Li et al. observed that the devil's club extract and fractions contained antiproliferative activities on specific human colorectal cancer cell lines, especially upon HCT-116 cell growth.

HPLC–MS analyses and bioactivities of novel chemicals in Devil's club (*Oplopanax horridus* (Sm.) Miq.)

(You, et al., 2012)

You et al. tested for total phenolic content (TPC), and antioxidant capacity of the dried root bark powder of devil's-club. The goal of this study was the identification of bioactive chemicals in Devil's-club root using HPCL-MS and the exploration of their bioactivities. The whole extract of the dried root contained TPC and strong ORAC and DPPH radical scavenging activities. You et al. also found that the extract exhibited a strong anti-proliferative ability against HT-29 cancer cells. You et al. concluded that the anti-proliferative activity of the plant may be attributed by the contribution of phenolic compounds.

HPLC-MS analysis

Eight phenolic compounds were identified:

1. Gallic acid
2. Caffeic acid
3. 4-O-feruloylquinic acid
4. 5-O-feruloylquinic acid
5. Methyl feruloylquininate
6. Ferulic acid
7. Methyl ferulate
8. Quercetin

The study concluded that the whole extract contained higher phenolic content than all other solvent extracts, also showing strong ORAC, DPPH free radical scavenging activity, and anti-proliferation activity. The chloroform extract contained a high amount of bioactive phenolics (see list) along with the ethyl acetate extract (responsible for DPPH free radical antioxidant activities).

2012 Unbiased evaluation of bioactive secondary metabolites in complex matrices.
Fitoterapia, 83(): 1215-1225

Inui, Taichi; Wang, Yuehong; Pro, Samuel M.; Franzblau, Scott G. and Guido F. Pauli

Complex natural products are characterized by a diverse set of secondary metabolites associated with a complex matrix (or background) that complicates the analysis of these metabolites. Many active principles are responsible for the biological activity of a medicinal plant. Crude natural extracts and its subfractions can be measured for potency, but synergistic interactions between the complex matrix must be considered when determining the source of activity. This study aims to explain their hypothesis that “the combination of high-resolution preparative fractionation, bioassay, analytical chromatography, and chemometric analysis enables the assignment of the bioactive constituents in the complex study material (ethnobotanical extract), without the necessity for isolation and/or full structure elucidation.” (1219) The moderate activity of the crude extract can be the result of highly potent compounds being present at very low abundance. For this matter, sensitivity is extremely important for the detection of bioactive metabolites.

By using biochemometric analysis, Inui et al. identified 100 active constituents among thousands of secondary metabolites in devil’s-club extract. The group identified three main compound classes and fourteen compounds active against tuberculosis.

Anticancer compound Oplopantriol A kills cancer cells through inducing ER stress and BH3 proteins Bim and Noxa

(Jin, et al., 2014)

In this study, Oplopantriol A, a polyne from *Oplopanax horridus* was found to kill cancer cells by causing stress to endoplasmic reticulum protein production. Jin et al. confirmed that Oplopantriol A preferentially kills cancer cells and inhibits tumor growth by interfering with the ubiquitin/proteasome pathway and inducing the expression of Noxa and Bim, proteins that regulate apoptosis.

Chemopreventive Effects of Oplopantriol A, a Novel Compound Isolated from *Oplopanax horridus*, on Colorectal Cancer

(Zhang, et al., 2014)

Zhang et al.’s study evaluates the compound Oplopantriol A’s activity against human colorectal cell lines HCT-116 and SW-480. In this study, the scientists used the xenograft colon cancer mouse model to evaluate chemo-preventative activities *in vivo*. They found that OPT A inhibited the malignant cells in a concentration- and time-dependent manner. Their data also showed that OPT A upregulates the expression of a cluster of genes, especially the tumor necrosis factor receptor and capsase families. Thus, Zhang et al. conclude that OPT A may induce apoptosis by upregulating these tumor necrosis factors and related pathways.

Inhibition of Human Pancreatic Cancer Cell Proliferation by Devil's Club *Oplopanax horridus* and Its Polyacetylene Bioactive Compound

(Cheung, Tai, Hasman, Ou, & Warnock, 2015)

Cheung et al. discovered that devil's-club shows dose-dependent antiproliferation effect on pancreatic cancer cells. The team reported antiproliferative activity of devil's-club 70% ethanol extract on pancreatic cancers with potent activity on genes PANC-1 and HP62. Cell cycle analyses show that devil's-club treatment on HP62 cancer cell resulted in S-phase arrest with minimal subG0/G1 apoptotic fraction and on PANC-1 caused G0/G1 arrest with a shift to S-phase and increased apoptotic fraction. In conclusion, Cheung et al. confirm the potency of devil's-club extract and fraction on pancreatic ductal adenocarcinoma cell proliferation and suggest that devil's-club compounds may be useful for pancreatic cancer treatment applications.

C. Collection of myths

The Widow and her Daughter

"There was a poor widow in a Tsimshian tribe who had a young daughter. All the people moved from the old village of Metlakatla, going to Nass River for the fishing-season. Then a strong wind blew, against the canoes. They could not go ahead on account of the north wind, which blew against them. They camped often, and this widow and her young daughter could not go on at all. They were left way behind the canoes, but they were still going on; and after all the canoes had left her behind, she camped at the foot of a high rock on a camping-ground. While they were in camp there, there was a severe storm during the night. They built a hut to shelter themselves during the stormy nights and days.

The first night when they were in camp the widow slept on one side of the fire, and her daughter lay down on the other side of the fire. At midnight some one came into the place where the young woman was, and touched her, and said, "Shall I marry you?" and the young woman agreed; and when the man came to her, she felt that something stung her body. Before daylight he went out again. The storm increased day by day, and the man came every night, and the young woman felt something like nettles stinging her body.

Every morning they found a partridge at her mother's door, and there was always sufficient fuel for them. One night when he came to her, he said, "We shall have a son, and he shall be a great hunter. There shall be no one like him, neither before nor hereafter, and I shall always be with him."

On the following morning it was perfectly calm. The widow went on to Nass River, and arrived there the same day when the fish arrived: and after the people had done their work of fishing, they moved back to the old village of Metlakatla. After they had been there a while, they moved to Skeena River for salmon fishing. The widow always had good success with the salmon and the berries she dried; and in the fall they moved down to the old town for the winter season.

"Now, when the time came, the young woman gave birth to a boy, a good-looking boy; and when the child was growing up, she went into the woods to get more fuel. There she met a young man, who said to her, "I came to visit you and my son. How is he?"—"Oh, he is a strong and fine boy." He said again, "When he comes to be a youth, do not give him too much to eat, but give him often devil's-club,' and let him chew some of the inner bark of devil's-club, and let him blow this in his hands, and let him rub it over his body after washing, and do not pass the place where I came to you first. I shall be with him, and he shall be a successful hunter in the future, and I will show him how to set traps and how to snare animals. Do not let him marry soon, when he is too young. Keep him unmarried."

After he had said so, he went away. Then the young woman went back home, carrying dry wood for the fire. Now, the child grew up rapidly and became a skillful hunter. One time he went to the mouth of Nass River with four of his friends, and they camped at the same place where his mother had camped on her way to Nass River when the young man had come to her on that stormy night. While his companions lighted a fire, this young man went into the woods; and when he went into the thick forest, he saw a man coming down in front of him, who said, "Are you my son?"

The young man was surprised at the words of the stranger. He stood there without speaking. The man who met him said again, "I am your father. I have come down to talk to you." The young man replied, "Then speak, father!"—"I will teach you how to obtain valuable animals by trapping them without shooting them," and he made a little trap. He showed him how to make it, and also how to make snares and how to bait wooden traps and skin snares; and he told him how many days he would have to observe taboos, and how many days he would have to fast and to wash. He continued, "And you shall eat the bark of devil's-club; and in the night, after you have counted four days, you shall wash on the bank of a brook and dive in the brook. You shall not wash your body for twelve months; then you shall dive in the stream twelve times, and every time after doing so you shall go in to a woman.

Then you shall get everything you want; but do not get married as long as you want to get riches, lest she be not true to you and you have bad luck. Do not marry soon, lest she be unfaithful! Count your days in months and years, and you shall be blessed; but if you lust for woman's beauty, you shall be poor. I will meet you once more." Thus spoke his supernatural father, and then he vanished from his sight. He did not see him any more.

The young man went back to his companions' camp. On the following morning, they went hunting, and he killed a great many animals. He did all that his supernatural father had told him, and all the animals of the woods heard that the young man was a very good hunter, and he was very successful. He made traps and snares for foxes and martens, and traps for grizzly bears and black bears, and so on; and every time he went out to look at his traps and snares, each trap and each snare had caught an animal, and he became richer than any one else.

Now another year came. Then the time of observing the taboos was ended, and he went up to set his traps and snares, and he made some more; and after he had finished he went home. After four days he went out again to see if anything had been caught, but there was nothing. All his traps had fallen and his snares had been broken.

The bait had been eaten out of the traps by the mice. He repaired them all and renewed the bait. He spent two days working, and then he finished and went home very sad. After four days he went up again, and he found nothing. All the traps and snares had been broken and the bait was gone. He repaired them and renewed his bait. He worked hard and went home full of disappointment. Early the next morning he went into the woods, looking for devil's-club, but he did not find any. Late in the evening he came back home; and after he had washed his body, he went up a little hill, and, behold! there was a large tree. He went toward it; and before he reached the foot of the large tree, a supernatural being came around to meet him. When he saw him, he said, "Is that you, my son? Tomorrow you shall cut down this large tree, which will last you throughout your lifetime." After he had said this, he disappeared.

The young man went home, and early the next morning he went and found the large tree. He went toward it, and, behold! there was a devil's-club tree larger than any other tree in the whole world. He took his stone ax and felled the great devil's-club tree; and after it was down, he took all the sap and bark and when he had collected it, he carried it down to his town and piled up the bark in his little hut behind his house. Then he started to wash his body with the bark of the devil's-club and its sap, and he ate some to purify himself.

He did so for forty days, and at the end of forty days he went hunting again. He repaired all his traps and snares. He went along for four days repairing his traps and snares; and on his way back from repairing his traps and snares, behold! a great Wolverine had thrown the traps and snares out of their places. Therefore the son of the Devil's-Club Tree pursued him, and the Wolverine ran as fast as he could; but the son of the Devil's-Club Tree ran faster; and when the great Wolverine was exhausted, he climbed a large tree, and the man who pursued him stood at the foot of the large tree on which the great Wolverine was sitting. The young man was about to shoot him, when he asked the Wolverine, "Did you break my traps and my snares? If you don't answer me now, I shall shoot you!"

The great Wolverine remained silent. The young man asked again, "Did you destroy all my traps and snares which I repaired so often?" Then the Wolverine began to cry. The young man said, "Answer me, or I shall shoot you! It is no use crying." Therefore the Wolverine had to say, "Yes, I did break your traps and snares." Then the young man said, "Will you give to me as many animals as I have lost through you? Wolverine did not want to answer the question. He was still crying. "Tell me how you became so great and successful in hunting! If you tell me, then I will let you go; if not, then I shall kill you." Then the Wolverine said, "I shall tell you, and you must let me go." Wolverine said, "I use devil's-club bark in my bath every morning, and I eat some."

The young man stood there; and when the Wolverine had spoken, he ran down from the tree laughing. So the young man pursued him; and when Wolverine was tired and weary, he climbed another tree; and the young man who pursued him came to the foot of the tree and asked him, and said, "Tell me what makes you so successful!"

Tell me quickly, or I shall shoot you!" Then the Wolverine said, "You shall eat the roots of the floating plants with their leaves." Again the Wolverine ran down from the tree laughing, and the young man pursued him.

Soon the Wolverine was tired out, and climbed another tree. The young man stood at the foot of it, and said, "If you don't tell me the truth this time, I shall shoot you right off!" Therefore the Wolverine was very much troubled, and said, "I shall let you know my secret.

You must eat a small piece of blue hellebore root; and when you bathe in the morning, use the hellebore roots to rub your body with. Then you will be successful." But the young man did not believe what the Wolverine told him, and said, "I don't believe what you tell me now. Tell me the truth, or I shall kill you right away!"

Then the Wolverine said, "You must take skunk-cabbage roots and eat a little of them, and use some when you bathe, and rub them over your body, as you did with the hellebore roots." The young man had not much confidence, but he let him go once more. As soon as Wolverine had run a little distance, he began to laugh again.

Now, the young man pursued him again. He ran faster than the Wolverine, so the Wolverine ran up a tree, and the young man spanned his bow and had his arrow ready in his hand. He pointed the arrow at the Wolverine without saying a word to him. Now, he said, "I shall shoot you right now." But the Wolverine said, "Wait, I shall tell you!" but the young man would not listen. He said, "I shall not wait any longer, because you have made fun of me three times." Then the great Wolverine said, "You shall have my secret now. It is the rotten fern (or qialu'>gAn ?)." Then the Wolverine began to cry, "Rotten fern!" and he went his way crying until his voice was lost.

Now, the young man went and repaired his traps and snares, and he made many new traps and snares, and he went and searched for some rotten fern (or qldlu°gAn%). He found some and ate some; and he used some while bathing in the morning, as the Wolverine had told him; and he came to be a great hunter, more successful than he had been before; and when he went to see his traps and his snares, behold! every one had caught a marten or mink or weasel, and many other good animals. He did so the whole year round, and in the spring he built bear traps, and snares for grizzly bears, and traps for wolverines and wolves and all other kinds of animals, and he became richer and richer. Many princesses wanted to marry him, and many times he gave a great feast to the people because he; was very rich. He remained an expert hunter.

Finally he married one of his uncle's younger daughters, and after many days his wife had a little son. When the boy grew up, he heard the people say outside, "There is a white she-bear coming down on the ice of the Skeena River!" and the son of Devil's-Club Tree took his spear and ran down. He saw the white she-bear coming down the river on the ice; but before he was able to throw his spear, the white she-bear kicked the ice, and the man was drowned. The white she-bear was almost drowned too, but she succeeded in reaching the bank. The man went under the ice and died there." (Boas & Tate, 1916, pp. 172-177)

The Origin of Devil's Club

"Devil's club has become not only a medicinal plant but also has purification powers used by the hunters. Many times hunters went out but returned empty-handed, because the animals were able to smell their scent and this made hunting very difficult. The people were in great hardship. They also had not observed fast days and purification periods.

One day a young prince who has a great hunter and who led a very clean life had been all over his hunting territory, but was unsuccessful in getting anything he hunted and finally was in great sorrow. No matter what he did, he could get no game. He came to his hunting camp in the hills, very discouraged and tired. Without eating he went to his sleeping place and dropped off to sleep. A vision came to him of a very beautiful young woman who came to where he was asleep and woke him saying, "My friend, I have seen your sorrow for a long time while and I pity you. I know you are discouraged because you have been unsuccessful in your hunting. Now I will show you

how you can be successful. First, you must be purified, and then animals will not smell your human scent. You must contact first a woman who is considered not only industrious and clever, but also a lucky woman, and just before you set off for hunting you will have several indulgences with this woman for four nights, changing to a different corner of the house each night until you have several connections with this woman in each corner of your house. You will not contact anybody else. Come I will show you." So the man in his visions had several indulgences with this beautiful woman who came to him in his vision. He slept with her and had sexual intercourse with her at each corner of the hunting house each night.

When he had finished, she said to him, "Now you have been with me four nights, you shall take this bark I give you and brew it and then bathe yourself and drink some of the brew. This you will do four nights at each corner. During all this time you must not contact any women, either to meet them or associate with them in any way. When you have completed four days in each corner, in order to purge yourself of its fatal influence, you again must indulge in sexual intercourse with the same woman. Then you do in the middle of those at the rear, or at your regular sleeping place. Then you again bathe yourself with the bark, rubbing it over the body. Then you leave for your hunting grounds. Be sure of the number of days and do not lessen or increase these, as these are your days. You must do the same with all your hunting paraphernalia. I am returning and I am devil's club and it is the bark of me that you will use."

The young man woke up and his vision was so realistic that he searched to find the woman that had appeared to him. He now returned to his village and not divulging his dream to anybody, when out and gathered much bark of the devil's club and put it in hiding. Then he went to a young woman who was considered very lucky, and also very clever and industrious, and said to her, "Come, I want to have sexual intercourse with you, and this is your fee." He had gathered considerable wealth as this woman was much in demand and was a very beautiful woman as well as of high rank. The first night the hunter slept with the lucky woman at the first corner and the next night at the second and the next night at the third corner and finally the last night at the fourth corner making a complete circuit of the house. Then he said to the woman, "I have finished with you and now when I want you again, I will come for you. In the meantime do not have sexual intercourse with anybody else until I am gone to my hunting again which will be some days hence." Next, the man took the devil's club brew and bathed himself thoroughly in the first corner of the house drinking some of the brew each day. This he did for four days in each corner. When he completed this he sent for the same woman with whom he had intercourse, and stayed with her in his regular sleeping place for one night. Next day, he again took his bath of devil's club brew. He now finished his purification and started out on his hunting. Right from first time he was successful. It seemed as if the game run towards him. He was so successful that when he returned he had much game. The people had come to him for instructions for training periods. There were many others who imitate, but one must observe control. Should one break a training day by missing a day in either sexual days or bathing days, the result would be a failure, and could even be a total failure for the trainee. This is the origin of the use of the devil's club for purification. Some training methods state that during the purging period, the trainee sleeps with the woman with whom he has had sexual days, but on his purging days in order to gain absolute self-control, he sleeps with the woman and plays with her body every day but as no sexual intercourse with her. This ensures absolute success." (Hudson, 1987)

Mrs. Harriet Hudson, Kitselas as recorded by William Beynon, 1947

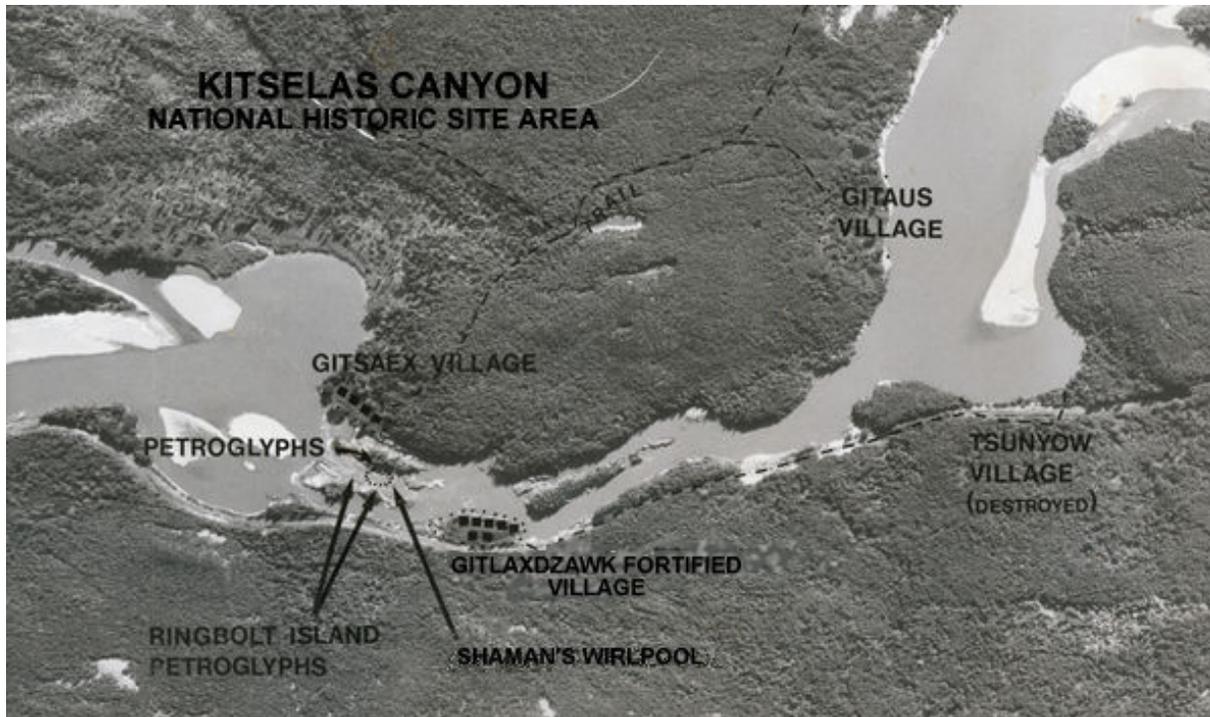


Figure 16: "This air photo of Kitselas Canyon and the Skeena River, indicates the five known village sites of the canyon. The earliest village sites are called Tsunyow, Gitaus and the Paul Mason Site. The word Tsunyow means 'the landing place.' Gitaus means 'the people of the sand bar.' This old village site was built beside a sand bar overlooking the Skeena River. The Paul Mason site is named after a Gitselasu elder who was part of the group that found the site in 1981. The site is on a wooded ridge and was lost from the memory of the Gitselasu. The knowledge of the other sites has been remembered by Gitselasu historians. The villages of Gitlaxdzawk and Gitsaex developed after Tsunyow, Gitaus and Paul Mason Site villages. Gitlaxdzawk is situated on what was a small island in Kitselas Canyon. The name of the village of Gitlaxdzawk according to the elder Paul Mason means the 'people of the place where they steal canoe bottom boards.' This name refers to the fact that the village was a fortress overlooking the river and enemies would have boulders thrown into their canoes. The name Gitlaxdzawk has also been given the meaning 'people of the ravine' and the 'fortress.' This village had ten large longhouses and many totem poles. The village would have been home to at least 300 people. The people were ravaged by a smallpox epidemic in the 1860s and 1870s. They vacated Gitlaxdzawk during that time. The village of Gitsaex is located opposite and upriver from Gitlaxdzawk. Both villages were occupied during the same time period and both communities were closely allied. The name Gitsaex means 'the people who live at the edge of the lake.' Gitsaex was a large village with seventeen longhouses and at least four if not five totem poles. The village was home to as many as 600 people. That village was also abandoned because of the smallpox epidemic of the 1860s and 1870s." <http://www.kitselas.com/index.php/about-kitselas/history/>

'The origin of 'wa'ums (Devil's Club), as a cure and use for purifications.'

'wa'ums is used by all the native people both as a medicine and purification purposes. Hunters before going on hunting trips would for many days drank a brew of the bark of devil's club and bathed themselves with the brew. This was to rid themselves of all human scents, as well as making the hunters very keen to see and builds his body up to make him light and swift-footed. During the time a hunter or a warrior or athlete are making these purifications they usually keep to themselves. They will have no sexual indulgences and keep away from contact with their wives or any females. Usually these preparations were carried over a period of time and in the house of one making preparation, he would begin his preparations at the corner nearest to the direction in which the sun rose and large quantities of the Devil Club brew, made from the inner or sap bark of the devil's club and also bathing himself with it, but a stronger brew. This would be done for four days, then he would move to the next corner in the direction of the traveling sun, (from East to west, or clockwise), and repeat the same procedure and then to next two corners of the house. Keeping himself from all the others. Some go into the woods for their purifications and would remain there for many days, until he was completely purified. When he went into the hills, there were many things his household must observe. First the females of the house must not go out and enjoy

themselves in their houses. But at night must retire to their sleeping place. They must not do any cleaning at night and especially clothes, if the hunters are expected to be away only a short while, they must not change their wearing apparel. The women must not indulge in illicit love affairs or sexual indulgences. Housecleaning is strictly tabu. There were other things, but another important thing was that all should drink as little water as possible, as this may cause storms.

“ All of these things the people learned from a young woman who had been taken by a super-natural being (*naxn'ox*) of the Devil's Club. In older days when the people were having difficulties in getting food, very often they met with periods of starvation and when this happened. The stronger people would leave for other places leaving behind the aged and weak. This is what happened, to an old widowed woman and her granddaughter who had just reached womanhood and was as yet a virgin. The old woman and her grand-daughter were now deserted not having any food and were alone. So they traveled along the shores away from where they were deserted in the hopes they could at least gather enough shellfish and beach food to keep them alive. They came to place where shellfish was always plentiful and in the woods they made a small lean-to hut and the young woman was able to gather dry fuel and with their fire drill they made a fire, and the young woman Then went to gather fuel to keep the fires going all the time. After this the young woman went down to the beach and brought up mussels and other shellfish which they now ate. Every day the young woman gathered fuel and also whatever foods she could. There was a scarcity of food and they could just get enough from day to day, to keep them alive and they were having great difficulties. When the weather was too severe they could not leave the hut they had built and barely kept alive. The old woman slept on one side of the fire and the young woman on the other side. They were now very hungry and all that they had been able to eat were some mussels that the young woman had been able to gather during the storm. Every day she was able to gather food fuel, bark she was able to take from the trees and in order not to perish, the fire had to be kept burning day and night. One night the young woman felt someone sleeping with her and embracing her, and then had intercourse with her, before daylight. This person disappeared, every night the young woman was visited and each morning she would go out and she would go out and she found a grouse outside, a goose, or some fish, such as halibut or salmon. They now were having plenty of food. Every night the young woman felt the presence of a man who slept with her and had intercourse and the woman could not know what kind of a man although she felt his body but other than he was a young man, he always left before daybreak and there was no way that she could find out who he was. The old woman who now had recovered her strength and she was now able to help the young woman who was enlarging the little hut they had built, so they could store the food which they were daily receiving. The young woman then told the old grandmother, “Every night we are visited by a young man, it is he that brings us the food we have such a good supply of, but I do not know who he is. How shall we find out,” Other than he must be a *naxn'ox* (supernatural being) nothing, more was known of him. But every day there was left outside the hut a carcass of something either a deer, seal, salmon, or geese. So that now there was now too much for the hut to store it. One night when the man came in and slept with the young woman, the young woman then asked, “Who are you that you are so good to us.” I have been sent by my father”, the young man replies, “who heard the crying of the old lady and sent me to teach you the way of Devil Club (*'wa'ums*) so that in the future the people will know what to do. “Next day the young man did not go away at day break as he usually did and he began to help to build a house in which to store all the food that they had and when this was finished the young man who never left the old woman and the young woman who was now his wife. When the house was complete and was now filled with food, the young man told his wife. “My father is the chief of the *'wa'ums* which you find all over the country is really a valuable plant and has many uses and which will bring good fortune to all that use it, as well as good health. Tomorrow I will take you and show you how to prepare this and will teach you its uses.” Next day the young man took the young girl into the woods and said showing her, “This is part of me and we call it *'wu'ums*. It has many uses and powers. It can cure many different ills and also can make one successful in anything one undertakes. You must scrape off all the thorns as these are very dangerous and can make you very ill. After you have scraped off the thorns and the top bark then you peel the inner bark in strips and fill a cooking vessel with these strips and then pour water on until all is covered and then boil it slowly. Drinking this as often as one wants keeps you in constantly pure. When preparing for hunting, you

must fast from other foods and act off all contacts with others of the house and bathe with the brew made from 'wa'ums. It can soon throw off all human scents and only the scent of 'wa'ums do the animals smell, and are not alarmed. But while using the 'wa'ums as a purifier you must observe the strict rule to keep away from any contacts while using it." The young man gathered some and carried it back to where they had built the new house and then he took their cooking vessel (a box) filled in with the inner (sap) bark of the 'wa'ums and filled it with water and placed hot stones in it and made it boil slowly. Then they gave some to the old woman, and immediately the old woman began to improve in health and was able to be?

One morning the young man spoke to his wife, "I must return to my father and I must leave you, now, that I have taught you the use of the 'wa'ums among the people. You must teach all the people so that it will help them to keep better and hunt better and be successful in all they do. But they must never disregard the tabus, connected with its use, as the spirit of the wu'ums will retaliate and the influence of the 'wa'ums will turn against him and instead of being successful, he will be defeated in everything he does. You will return to your people and teach them what I have taught you they will also teach all the other tribes." After this, the man disappeared and only the two women were left. They now had a large supply of food and also a canoe. The young woman went into the woods and with the knowledge her husband had given her, she gathered a large quantity of devil Club and filled many baskets that the old woman had made.

The people who had deserted the young woman and grand-mother now returned to their village of Metlakatla and the chief wondered what happened to his relatives they had deserted, so he said to the tribesmen go to the nearby camp at K'met-Ku and if anything can be found of their remains cremate them. The must have perished from starvation." So the tribesmen set off and behold when they came to camp, they saw a large house and they landed below this and going up they found the young woman and her grandmother both very busy preparing food. They saw that the house was filled with foods of many kinds and were somewhat embarrassed and the young woman said. "You have come from my uncle and since we have come here, we have learned much since we have come here. Many things that will benefit not only my uncle, but all his people, so that they shall become the most prosperous people on earth." Food was given to her uncle's tribesmen and some to take back with them for her uncle. When they returned the spokesman said, "We were astounded at the wealth of the young woman and her grandmother they have a large house which is full of all different kinds of food, sea and mountain foods, and all kinds of strange bark. Your niece and her grandmother told us that they have something which will make us the most powerful people of all the other tribes. She told us no more, so we advise you that you should go and fetch them here to your house."

The chief at first feeling embarrassed, finally he called together his people and said, "We will go at once and bring them here." The set out with his tribe and landing where the young woman and her grandmother were living and then the chief said to the women, "I have now come with my tribe, to fetch you to your own house and we take all your belongings." They then packed all that was in the large house into many canoes and then set off their village at Metlakatla.

When they had settled into the house of the great chief, the young woman, they gave a feast to which the uncle's whole tribe were invited into the house and then the young woman spoke to them. "While we were at 'Kmetku, a supernatural being visited and helped us and he had been sent by his father who was the chief of the 'wa'ums. He first gave us plenty of food and then built the large house that you see. Then he also showed us the 'wa'ums plant and all its uses and powers and how to prepare it and what its powers are to be used for. For purification purpose it must be used in such a way and respect, so that its powers will not flare back on the one using it. It will purify a hunter so that the animals are unable to smell the human scents, smelling only the 'wa'ums scent. Also, this 'wa'ums is to be used in times of sickness for many ills. All of these things the supernatural being has shown me and I will now teach you all the showed me, then we, in turn, can do this to all the other Tsimshian tribes and in doing so we can lead them all." So the young woman taught all of her people the uses of the 'wa'ums. Also, she showed them the method of purifications and that during this period that they must keep away from contact

sexually with each other. In a short time the people began to know of its use of the 'wa'ums and its powers and soon their hunters were very successful and the tribe now always had plenteous supplies of food and other wealth, so now they began to be called upon by the other tribes to teach them the uses of this 'wa'ums. This is the story of the origin of the 'wa'ums. (Devil's Club)

P Ryan Metlakatla (1952, p. 39-47)

The Arrow Chain

Two very "high-caste" boys were chums. They used to make great quantities of arrows and play at a smooth, grassy place on top of a hill way back of their village. On a moon-lit night, they started, as usual, for their playground. Along the way, as the lesser chief's son was joking about the moon, suddenly it became very dark about them. The head chief's son saw a ring about them like a rainbow. When it disappeared, his companion was gone. He called to him but did not get any response; he ran up the hill but did not see him there either. The moon must have gone up with him, he thought. Left alone, he sat down and cried, after which he began to try the bows. He shot an arrow at a large and very bright star next to the moon, when the star darkened. He kept shooting at the star from the big piles of arrows they had made until he saw something hanging down very near him like a chain of arrows reaching down to him. As he felt badly for the loss of his chum, lying down under the arrow chain, he went to sleep. After a while he awoke, found himself sleeping on that hill, remembered the arrows he had shot away, and, looking up, he saw a long ladder reaching down to him. Taking various kinds of bushes, he stuck them into the knot of hair he wore on his head, climbed up the ladder all day, and camped at nightfall upon it. When he awoke the next morning his head felt very heavy; he seized the salmonberry bush that had been in his hair, pulled it out, and found it was loaded with berries. After he had eaten the berries off, he put the branch back into his hair and felt very much strengthened. (This he repeated at noon with blue huckleberries, and the following morning with red huckleberries.)

By the time he had reached the top, he was very tired. He saw a large lake and lay down there to sleep. While he slept, a little girl shook him awake, saying that her grandmother had sent her to bring him her house. At the grandmother's house, upon hearing of his quest of the lost companion, the old woman told him that his friend was next door, in the moon's house. Then the old woman gave him food. After that she gave him a spruce cone, a rose bush, a piece of devil's and a small piece of whetstone to take along.

As he approached the moon's house, he heard his friend screaming with pain on a high place near a smoke-hole. The boy reached down through the smoke-hole, pulling his friend out; and meanwhile, putting the spruce cone down where his friend had been, he told it to imitate the friend's cries, and away they ran. Later, as the cone dropped from its place, the people discovered that their captive had escaped. The moon started in pursuit, at which the boy threw the devil's club behind them and a patch of devil's club arose, which the moon had much trouble getting through. As the moon approached them again for the second and the third times, the boy threw back the other objects, which helped delay the moon's pursuit; the grindstone, in particular, kept the moon rolling back.

The boys now reached the old woman's house. She gave them something to eat. When they were through, she said, " Go and lie down at the place where you lay when you first came up. Don't think of anything but the playground you used to have." They went there and lay down, but after some time the boy who had been a captive of the moon thought of the old woman's house and immediately they found themselves there. Then the old woman said, " Go back and do not think of me anymore. Lie

there and think of nothing but the place you used to play." They did so, and, when they awoke, they found themselves on their playground at the foot of the ladder.

As the boys lay there, they heard a drum beating in the house, where a death feast with dancing was held for them in the evening. They waited until the feast was over and the people were away. As they stood at a corner of the house, the boy's younger brother came out, who recognized him and brought news to his mother that his brother and his friend were out there. The mother was not convinced (she said, "Don't you know your brother had died some time ago? ") until her younger son brought in a piece of his brother's shirt. They sent words to the parents of the lesser chief's son and to all of the village houses. Then all the people of the village came to see the boys." (Yen, 1980)

From Stith Thompson's *Tales of the North American Indians*

Process for Making Devil's Club Tonic (*Ts'-iihlanjaaw*) by Robert Cogo- Haida (p. 29-33)

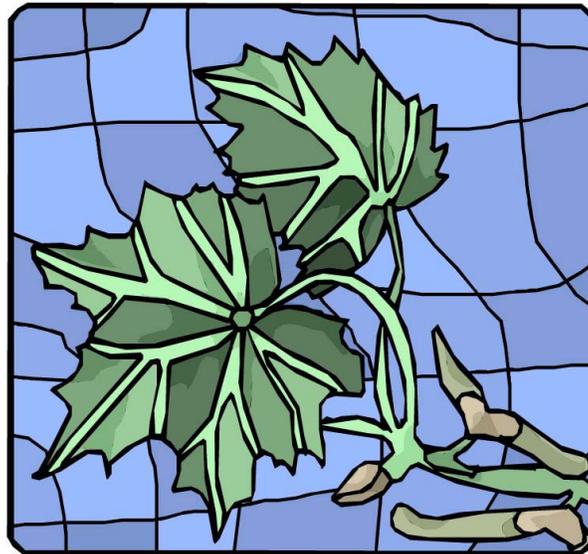


Figure 17: *ts'iihlanjaaw*

I have written about it in the Haida language (*Xaadas kíl*) and it went over big. I am an old hand at making Devil Club (*Ts'-iihlanjaaw*) medicine (*xíl*). Ed Cogo, my father (*kúsh waan*) taught me the process in my youth. In 55 years, I have probably made over two thousand (*láagwa-tlaláay-sdá*) gallons all total.

This medicine (*xíl*) is used quite a bit and doctors who had it analyzed found it a very good blood purifier. This one thing is big in itself. Haida (*Xaadas*) in the old days used it extensively. The Haida custom calls for a person of the opposite phratry making the medicine for ones use. Say an Eagle (*Ts'áak*) would make the medicine (*xíl*) for a (*Yáahl*) or Raven. In my case I am Eagle would make the medicine (*xíl*) for my wife who is Raven. Before I take a case we go through a little ritual of token payment (*gáad gín xa'áaw*) native custom.

First, a person has to believe in it and what the Devil's Club (*Ts'-íihlanjaaw*) will help.

Second, the one making the medicine (*xíl*) also has to believe in its use fully.

Third, the person who is to receive the medicine usually puts down a few dollars as token payments. This is also called (*gáad gín xa'áaw*) one of the rituals. I will tell about how I go about making the medicine (*xíl*).

I go out in the morning looking for a good stand of Devil's Club (*Ts'-íihlanjaaw*). A good place to look is near the beach (*cháaw salii*) facing strong southeast winds (*xíkw*). This has the benefit of sea spray enriching the soil (*tangáa*).

In the old days, a large knife (*ya'áats*) was used to cut the stock. After you cut down a few stocks about five or six feet long, you cut it up into lengths of about eighteen inches (*tlaáhl waak sdáansaangaa*). This is a good way to fill up a box. Now-a-days I use a brush cutter and thick rubber gloves (*stlahl k'únk*).

Next, I go home with the stock. I get two boxes, one for scraping residue and the other for the inner bark which is the one I boil. I use the back side of an old butcher knife (*taakadáaw*) to scrape off the sharp prickly thorns and the outer grey bark (*k'uts*). You follow this process till all the stock is used up. For a box full of stock I get enough savings for about three boilings. I use a three-gallon pot (*gan*) or container to boil the bark (*k'uts*). For a blend and to enrich the medicine (*xíl*) I put in three different sprouting trees about 8 inches long. One spruce (*kíit*), one cedar (*ts'úu*), and one hemlock (*k'áang*). You pull these up roots and use all of it. You wash these under a faucet and boil with the Devil's Club (*Ts'-íihlanjaaw*). You start with two gallons of cold water (*g'ántl*) in the pot (*gan*). Add two hands full of Devil's Club (*Ts'-íihlanjaaw*) bark and the three small trees. Note: Some makers put in some alder bark (*kál k'uts*) for color and flavor (*k'ústgat láa*). Bring to boil and simmer three hours (*k'asgat hlgúnahl*). Cool and put into half gallon jars (*káalk*) and keep in cooler. One cup full three times a day does the trick. Those who drink this medicine (*xíl*) swear by it. Drink (*Ts'-íihlanjaaw*) for health. (*Ts'-íihlanjaaw hl níihl*). Thank you (*haawaaw*)."

Map of the Salish Sea



<http://uvac.uvic.ca/gallery/salishcurriculum/files/2015/02/SalishResourceGuidemap-e1428705447696.jpg>

Figure 18: Map of Coast Salish territories (in green) with language groups (in red). Map by Deborah Reade.

(anywhere I go, you go my dear; and whatever is done
by only me is your doing, my darling) e.e. cummings