ETHNOBOTANICAL INVESTIGATION OF PLANTS USED FOR THE TREATMENT OF TYPE 2 DIABETES BY TWO CREE COMMUNITIES IN QUÉBEC: QUANTITATIVE COMPARISONS AND ANTIOXIDANT EVALUATION

by

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ABSTRACT

This ethnobotanical project screened and evaluated the use of traditional medicine of the Cree Nation of Quebec as part of a study directed at preventing complications associated with Type 2 diabetes (T2D). Antidiabetic plants used by the Cree that treat T2D symptoms were identified. Quantitative ethnobotany and analysis of antioxidant activity were conducted. Results from Whapmagoostui were compared with those found in Mistissini and also the literature. Twenty-one plant species were cited during the survey. Although Cree medicine throughout Québec and Canada is homogenous, geographical and vegetation gradients show some variations. Medicinal plants have better antioxidant potential than non-medicinal plants and have a higher phenolic content. Rankings based upon the ethnobotany, the bioassays and the quantitative tools showed positive correlations. This evidence supports the beneficial effects of Cree TM and medicinal plants selected by the Cree Nation in the prevention of T2D and its complications.

RÉSUMÉ

Cette étude ethnobotanique a étudié la médecine traditionnelle utilisée par la Nation Crie du Québec. Elle s'intègre à un projet voulant prévenir les complications associées au Diabète Type 2 (DT2). Les plantes médicinales Cries reliées aux symptômes du DT2 furent identifiées. L'ethnobotanique quantitative et l'activité antioxydante furent mesurées. Les résultats de Whapmagoostui ont été comparés à ceux de Mistissini et ceux tirés de la littérature. Vingt et une plantes médicinales ont été mentionnées. La médecine crie reste homogène au Québec et au Canada bien que des gradients géographiques et floristiques entre les communautés ont montré des différences dans l'utilisation des plantes traditionnelles. Les plantes médicinales possèdent des propriétés antioxydantes supérieures aux plantes non médicinales et une quantité plus élevée de composés phénoliques. L'information des Aînés, de l'ethnobotanique quantitative et des bio-essais fut corrélée. La médecine traditionnelle Crie suscite certaines évidences quant aux effets bénéfiques de son utilisation pour la prévention du DT2 et ses complications.

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CONTRIBUTIONS OF AUTHORS

The manuscripts were written by the first author under the guidance of both supervisors, Dr. Timothy Johns and Dr. Alain Cuerrier. They advised on the objectives and the data analysis.

Several participants contributed to the realization of manuscript I: Jànos Podani contributed with the Podani algorithm; Charles Leduc and Sonia Grandi contributed to the collection of plant material in 2003 and 2004 at Mistissini, respectively.

In manuscript II, Patrick L. Owen explained to the author how to conduct the protocols of DPPH, TBARS and CD assays. Finally, John T. Arnason, with the collaboration of San Nguyen, measured the total phenolic content of the plant species.

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LIST OF ABBREVIATIONS

AGE: Advanced Glycation End product
BHT: Butylated hydroxytoluene
CA: Cluster analysis
CBHSS: Cree Board of Health and Social Services
CCELC: Canada Committee on Ecological Land Classification
CD: Conjugated Dienes
CEI: Cree of Eeyou Istchee
CT: Consensus test
$CuSO_4$: Copper
DPPH: 1,1-diphenyl-2-pycryl-hydrozyl
EDTA: Ethylenediaminetetraacetic acid
EtOH: Ethanol
GPS: Global Positioning System
HBC: Hudson's Bay Company
HPLC: High-Performance Liquid Chromatography
LDL: Low-Density-Lipoprotein
LSD: Least Significant Differences
MDA: Malondialdehyde
MeOH: Methanol
$Na_2HPO_4.H_20$: Sodium phosphate monobasic monohydrate
Na_2HPO_4: Sodium phosphate diabasic anhydrous
NaOH: Sodium hydroxide
OTU: Operational Taxonomic Units
PBS: Phosphate Buffer Solution
ppm: parts par million
ROS: Reactive oxygen species
SIV: Sydromic Importance Value
T1D: Type I Diabetes or insulin-dependent diabetes mellitus
T2D: Type II Diabetes or non-insulin-dependent diabetes mellitus
TBA: Thiobarbituric acid
TBARS: Thiobarbituric Acid Reactive Substances
TCA: Trichloroacetic acid
TM: Traditional Medicine

1.0 Introduction

In recent times, Type 2 Diabetes (T2D), previously called non-insulin dependent diabetes mellitus, or type B, has become an enormous world health problem, with 171 million cases reported. The problem is now considered to be an epidemic (World Health Organization 2005). In 1995, 1,174,000 people had glucose intolerance (Amos *et al.* 1997). The prevalence of diabetes has increased among several countries throughout the world, including Canada, and has reached 2.8 % of the worldwide population. Predictions estimate that the increasing rates of T2D will lead to an alarming 366 million cases by 2030 (Wild *et al.* 2004).

Brassard and Robinson (1995) reported that T2D was once rare in Canadian First Nations populations but has increased dramatically in the past half century. The prevalence of T2D is found to be 3.6 and 5.3 times higher among First Nations men and women, respectively, than the general population of Canada (Brassard *et al.* 1993; Health Canada 2005).

More specifically, T2D has spread throughout the Cree communities in both the James and Hudson Bay regions in Québec, the Cree of Eeyou Istchee (Robinson 1988; Brassard 1991; Brassard *et al.* 1993; Dannenbaum *et al.* 1999). The Cree Board of Health and Social Services (CBHSS) (2001) has reported that the disease affected approximately 975 people of Cree origin in Québec. The proportion increased from 4.1 % (1989) to 12.7 % (2001) in comparison to 7 % in the rest of the Canadian population. Environmental and genetic influences, such as sedentarization, socio-economic changes and industrialization predispose Indigenous communities to T2D (Hoffer *et al.* 1981; Young and Sevenhuysen 1989; Brassard 1991). Modern European and Western approaches have attempted to treat diabetes and its complications among Indigenous people through dietary intervention strategies and programs of diabetes prevention (Boston *et al.* 1997; Gray-Donald *et al.* 2000; Bisset *et al.* 2004). Despite these efforts, among Cree of Eeyou Istchee, T2D is still on the increase.

To find alternative avenues for preventing diabetes, it is important to examine the possibility of working in harmony with Cree communities by using their cultural and traditional approaches to medicine and healing. In this context, the Cree of Eeyou Istchee, under the guidance of their Elders and Healers, have used plants from the regions they inhabit as therapeutic aids for symptoms associated with diabetes for the last 2000 years (Holmes 1884; Strath 1903; Beardsley 1941; Black 1978 and 1980; Blacksmith 1981; Moerman 1998; Oubré *et al.* 1997; Young *et al.* 2000; McCune 1999; McCune and Johns 2002 and 2003). A 2003 collaborative research project resulted in ethnobotanical data of eighteen potentially antidiabetic plants gathered from a Cree community in Mistissini, located in the boreal forest of northern Québec (Leduc *et al.* 2006). To conduct this ethnobotanical research, anthropological, botanical, ecological and pharmacological studies were applied (Alexiades 1996; Balick and Cox 1996; Cunningham 2001). However, besides Leduc *et al.* (2006), no other ethnobotanical work has documented antidiabetic plants used by the Cree in Whapmagoostui, a coastal community situated in eastern Hudson Bay. Furthermore, since the work of Leduc *et al.* (2006) on comparative and quantitative ethnobotany with Cree-specific literature in Canada, no work has compared ethnobotanical and analytical data between different Cree communities of Québec.

Both T2D complications and hyperglycaemia have been linked with oxidative stress, related to the presence of reactive oxygen species (ROS) (Baynes 1991; Giugliano *et al.* 1996; Scheffer *et al.* 2005). For example, oxidative stress causes lipid peroxidation of low-density-lipoproteins (LDL). However, antioxidants can counterbalance some of the effects of oxidative stresses by preventing oxidative modification of LDLs (Duvall 2005). Marles and Farnsworth (1995) have stipulated that antioxidant compounds from different medicinal plants used by Aboriginal communities and people may play a role in the prevention of this disease. McCune (1999) reported that Canadian indigenous medicinal plants have higher antioxidant properties than commercial products, and also have the potential for preventing and/or treating T2D symptoms. Antioxidant properties of plants are also associated with high polyphenol levels (Cai *et al.* 2004; Katsube *et al.* 2004; Lee

et al. 2004). To date, however, researchers have not looked at the antioxidant potential and phenolic content of traditional antidiabetic plants used by the Cree of Eeyou Istchee.

New approaches and further examinations of traditional medicine (TM) and medicinal plants could prove helpful in preventing continual T2D prevalence among the Cree people. Furthermore, ethnobotanical studies could be beneficial to select TM and antioxidant measurements could be used to validate the potential of treatments historically used by the Cree population. Even if some traditional knowledge has disappeared, the Cree can be given the opportunity to continue the use of TM. This would not only be beneficial in order to preserve cultural knowledge and values, but also to help prevent T2D expansion as well as to be acknowledged for the use of successful TM treatments in future work on T2D prevention.

2.0. Literature review

2.1. Diabetes mellitus

Diabetes is a chronic disease characterized by hyperglycaemia caused by lower plasma insulin secretion or action and higher than average glucose concentration in the blood commonly due to a problem with inlet β-cells in pancreatic tissues (Bennett *et al.* 1992). Perl (1987) reported that the disease is associated with long-term damage of the pancreas and the change in insulin prevents the absorption of glucose from the blood into cells.

Many authors have described the classification, symptoms and the complications of diabetes mellitus (West 1978; Zimmet 1982; Arky 1983; Bennett *et al.* 1984; Young 1987; Walther *et al.* 1991; Marles and Farnsworth 1995; American Diabetes Association 1996; Amos *et al.* 1997; Anonymous 2002; International Diabetes Federation 2003; World Health Organization 2005). Type 1 diabetes (T1D) is categorized by the failure of the β-cells in the pancreas to secrete insulin. T2D is characterized by resistance to insulin action with relative insulin deficiencies, high blood sugar levels and obesity. T2D is diagnosed in 85-90 % of all diabetes cases. Symptoms include polyuria, polydipsia, sometimes accompanied by symptoms such as blurred or loss of vision as well as many others described by McCune (1999). This chronic disease has long-term complications,

such as kidney failure, eye problems, stroke, neuropathy and even premature death. These ailments highly compromise the quality of life of diabetic patients and create the need for serious medical intervention and care. Finally, this chronic disease alters copper, zinc, magnesium and lipid peroxidation.

2.1.1. T2D and Indigenous people

Dannenbaum *et al.* (1999) identified diabetes as one of the most urgent health conditions that Canadian Indigenous people confront. Indigenous people around the world have also been affected by T2D. For example, among Native Americas with T2D (Gohdes 1986; Szathmary 1994), Oklahoma tribes have been particulary affected with a dramatic increase for at least the past 50 years (West 1974, 1978), as well as have the Pima tribes (Bennett *et al.* 1971). Furthermore, T2D is present among Aboriginal people in Canada (Daniel and Gamble 1995). The prevalence of T2D among these communities is three to five times greater than among the general population of Canada (Health Canada 2005).

2.2. Cree Nation

In Canada, the Cree are situated along the boreal forest in Québec, Ontario, Manitoba, Saskatchewan and Alberta (East Cree Language 2005). The Cree of Eeyou Istchee in James and Hudson Bay, Québec, represent the regional subpopulation of the Canadian Cree Nation. They have inhabited the regions in both the James and Hudson Bay for 5000 years and form a population of 14,600 Crees (Secrétariat aux affaires autochthones 2005). Along with the Algonquins, Attikamekw (*Tête-de-Boule*), Innus and Naskapis, the Cree are part of the Algonkian language family from the subarctic region and form the algic family (Hydro-Québec 1993b).

Traditional life of Cree families was nomadic, which included a lifestyle with high physical activity, no recorded history of chronic disease, and a healthy diet including fish and plants (Brassard and Robinson 1995). With cyclical inland travelling, the Cree historically exploited the taiga more in continental areas and riverside environments (Hydro-Québec 1993b; Duhaime 2001). Once a year during the summer season all family regrouped around the trading posts to trade furs, purchase supplies and to harvest beluga whales (Robinson 1988). These groups travelled north, where they were familiar with a

variety of northern habitats, and adapted successfully to their environment (Kuhnlein and Turner 1991). Natural resources were essential to survive (Kuhnlein 2000) and often played a role in treating various diseases (Holmes 1884; Marshall 1984).

2.2.1. T2D and Cree people

The Cree of Eeyou Istchee have the highest prevalence of T2D (Brassard *et al.* 1993; Young *et al.* 2000) in contrast with other Cree communities in the rest of Canada (Young *et al.* 1985). Young and Sevenhuysen (1989) reported no cases of T2D in 1976 but twenty-two cases in 1986. T2D has increased exponentially among Cree of Eeyou Istchee, and the CBHSS (2001) has recently counted 975 cases. It is possible that this rate has probably increased in 2006.

The proportion of T2D among the nine Cree communities of Eeyou Istchee decreases as one moves from the southern to northern communities. Disease rates are 18.3 % in Waswanipi, the most southern village of Cree of Eeyou Istchee, compared to 6.3 % in the most northern community of Whapmagoostui. Mistissini is situated between those villages, where 14.1 % of the population have T2D (CBHSS 2001). The differences in T2D rate could possibly reflect the distance between these communities and the non-native populations that inhabit the regions in the southern communities (Maberley *et al.* 2000). Whapmagoostui, for example, has a population that has less contact with non-native people and traditional practices are preserved more successfully (Adelson 1992).

2.2.2. Genetic and environmental influences

The rising rates of T2D among the Cree of Eeyou Istchee is due to the introduction of environmental influences which have led to a change in the traditional lifestyle as well as the effects of industrialization in conjunction with genetic factors (Barger 1971; Young 1987 and 1990; Brassard 1991; Harris *et al.* 1997; Young *et al.* 2000). For example, Rousseau (1945) reported his observations on the history and social changes experienced by the Cree of Mistissini, located in the southern inland boreal forest in James Bay. Rapid social changes from Western European influences have also had effects on Cree communities in different regions (Young *et al.* 1985; Braroe 2002; Hegele *et al.* 2003)

and Indigenous communities throughout the world (Prance and Kallunki 1984; Gohdes 1986; Prance *et al.* 1987; Diamond 1992).

Adelson (1992) explains the chronological events of Cree history, especially in Whapmagoostui. The first Western influences in Whapmagoostui (Kuujjuaraapik, Great Whale River or *Poste-de-la-Baleine*), a coastal Cree community of Eeyou Istchee, began in 1732 with Anglican missionaries, traders from the Hudson's Bay Company (HBC) and Western European explorers (Balikci 1961; Marshall 1984; Bobbish and Magonet 1990; Hydro-Québec 1993b). For the purpose of clarity, environmental stresses introduced among the Cree modified their traditional lifestyle. Environmental influences are taken to broadly include factors such as demographics, socio-economic changes in family and community structure (religion, degree of modernization, psychosocial stresses) or physiological changes (sedentarization, dietary, obesity) (Zimmet 1982; Bennett *et al.* 1984; Bennett *et al.* 1992; Maxwell 1995). More specifically, Young and Sevenhuysen (1989) and others have reported that sedentarization, poor diet and obesity predispose residents of Cree communities to T2D (Hoffer *et al.* 1981; Brassard 1991).

As Zieba (1992) and Braroe (2002) have described of the Canadian plains, missionary culture and institutional life influenced traditional Cree lifestyle by modifying traditional beliefs in nature. Anglican missionaries established settlements close to the trading post of Whapmagoostui in 1876 (Balikci 1961). Today, Christianity is prevalent in Cree society. Now that the Cree people believe in God, who is the creator of plants and animals, and have adopted Christianity and the religious culture associated with certain European influences, a part of traditional pre-Christian belief in nature has been lost and bush skills are barely surviving (Ohmagari and Berkes 1997). The HBC established a permanent fur trading post at Whapmagoostui, which created more socio-economic influences on traditional lifestyles (Barger 1971, 1978). Later in 1955, the Canadian army arrived in the community and intensified inter-ethnic conflicts (Balikci 1961). Anthropological studies of Whapmagoostui Cree have concluded that the acculturation of the community, construction of new and different infrastructures, programs, economy and, indirectly, federal and provincial projects such as the Hydro-Québec dam project,

have further influenced Cree culture (Honigmann 1962; Balikci 1961; Barker 1971, 1978; Adelson 1992; Hydro-Québec 1993a, b).

From the environmental influences previously described, the Cree gradually made changes to their nomadic lifestyle in order to spend more time in Whapmagoostui to exchange game for flour, sugar, cloth, tea, guns and ammunitions (Robinson *et al.* 1995). In 1940, government benefits were introduced in Cree communities and administered in particular localities, again spreading the affects of sedentarization and disrupting traditional lifestyle habits. The movement from bows and arrows to knives and guns (Robinson 1988), coupled with new commercial pressures resulted in the overexploitation of big game (Berkes and Farkas 1978). This has led directly to the introduction of the European diet due to the over-hunting of wild meat. Now, the Cree diet has certain nutrient deficiencies (Berkes and Farkas 1978) such as carotenoid deficiency (vitamin A or β-carotene), ascorbic acid (vitamin C or ascorbate) and α-tocopherol (vitamin E). These vitamins are all natural exogenous antioxidants that can be found in Cree traditional foods. Malnutrition is now also a problem among the Cree of Eeyou Istchee, similar to other First Nation peoples in the rest of Canada (Moore *et al.* 1946; Vivian *et al.* 1948).

Santé Québec (1998) has documented that a major portion of Cree youth today, similar to other North American adolescents, eat commercial foods that contain a high proportion of sugar compared to traditional foods, while only 15 % are still hunting and eating wild meat (Young *et al.* 2000). In comparison, for Crees men and women born before 1940 to 1960, to be 'in health' means to eat the products of 'land, water and sky'. Thus, the older Cree prefer to eat traditional food than commercially bought food (Adelson 1992).

Finally, Young and Sevenhuysen (1989) have reported that the prevalence of obesity has been seen to increase among the Cree with age, along with the duration of diabetes and also ischemic heart disease. Lavallée and Bourgault (2000) have found that a large proportion of Cree suffer from obesity (four in five adults), especially women and particularly those in Québec (Thouez *et al.* 1990). The CBHSS (2001) has reported that

94 % of the Cree of Eeyou Istchee with diabetes are also overweight. Combined with other risk factors, including a lack of physical activity or malnutrition, obesity has become the most important consequence of diabetes-related illnesses (Bennett *et al.* 1984; Bennett *et al.* 1992; Young 1987 and 1990; Harris *et al.* 1997).

Additionally, there are genetic components in relation to T2D such as insulin gene polymorphism (Young 1987). Moreover, Neel (1962) has underlined the 'thrifty' gene, a genotype that converts glucose into fat during famines, as a genetic link to symptoms associated with T2D that has caused a higher prevalence among Aboriginal people (Bennett *et al.* 1971; Robinson 1988; Diamond 1992). It is also of interest to note that the thrifty genotype is higher among women than men (Young *et al.* 1985; Maberley *et al.* 2000).

Despite these modern Western European influences that have caused health problems, some Cree Elders and Healers still practice traditional activities and medicine (Hydro-Québec 1993b), although the younger generations have mostly stopped praticing those activities (Young *et al.* 2000).

2.2.3. Traditional medicine

Elders and Healers from different First Nations exploited medicinal plants and fungi to treat diseases (Adelson 1992). An Elder is defined as an older person respected by the community due to his or her knowledge of traditional ways of life. A Healer follows traditional health practices in-keeping with available natural resources. Scott and Receveur (1995) have suggested that both Elders and Healers were the prime sources of knowledge and those with the most experience of traditional remedies in the forest (Zieba 1992; Cox and Balick 1994, Phillips and Gentry 1993a, b). Traditionally, information from Elders was passed on to the community and the next generation through an established oral tradition, education, and through the demonstration of practices and spiritual powers (Schultes 1978; Bobbish and Magonet 1990; Zieba 1992; Cox and Balick 1994; Marles *et al.* 2000; Martin 2004) and the practice of story telling (Masty 1998).

TM, which includes use of plants, has an important role to play in the treatment of T2D. Marles and Farnsworth (1995) have listed 1200 species of plants that are used to treat diabetes and among those that were investigated 80 % showed antidiabetic properties. McCune and Johns (2003) reviewed different plant parts, such as buds, flowers, leaves, fruits, nuts, seeds, roots, bulbs, rhizomes and inner bark (cambium) that are used among First Nations communities in Canada to treat T2D symptoms. Medicinal plants are also used among the Cree. 88 plants were known for their benefits to Cree Healers and Elders. Of these, 81 species could be located in Québec (Holmes 1884; Strath 1903; Beardsley 1941; Erichsen-Brown 1979; Black 1980; Arnason *et al.* 1981; Blacksmith 1981; Zieba 1992; Moerman 1998; McCune 1999; Haddad *et al.* 2001). Most of these plants are found in the boreal forest, rather than in the northern area of eastern Hudson Bay where few ethnobotanical studies have been done. In Mistissini, a study done to identify medicinal plants used by the Cree of Eeyou Istchee to treat T2D symptoms found eighteen plant species (Leduc *et al.* 2006). This is the first ethnobotanical study on antidiabetic plants in Québec among the Cree of Eeyou Istchee. An extension of this work to other communities could enrich knowledge and create a more comprehensive understanding of available ethnobotanical information.

2.2.4. Ecoclimatic regions

Elders and Healers of the Cree of Eeyou Istchee discovered plant remedies among northern territories by exploring the vegetation of inland forests in which their communities were located (Barger 1971, Black 1980; Zieba 1992). Scott (1995) classified the vegetation of the vast northern territories of Québec in different zones, depending on various factors such as coastal or inland region, latitude, climate, and other environmental factors. According to Payette *et al.* (2001) Whapmagoostui and Mistissini are situated in two different ecoclimatic regions; hemiarctique and boreal, respectively (Appendix 1).

Whapmagoostui, in the south-eastern corner of Hudson Bay, has both coastal and continental vegetation characterized by an irregular transition between the boreal continuous forest and the Arctic tundra. The Canada Committee on Ecological Land Classification (CCELC) (1989) characterized this coastal area as the mid-subarctic ecoclimatic region. This region contains a discontinuous forest on open territory caused

by exposure to frequent fires (Hydro-Québec 1993a; Scott 1995; Bergeron *et al.* 2001; Parisien and Sirois 2003). Therefore, trees seem to be shrivelled up (e.g., Krummholz). There are few flowering plants species due to the short summer season of only five months (Ducruc 1976; CCELC 1989). Scott (1995) and Hydro-Québec (1993a) documented that the dominant trees are *Picea glauca* and *Larix laricina*. These species decrease in prevalence with distance from the coast until they are completely replaced in continental inland areas by stands of black spruce (*Picea mariana*). The hilly landscape of the plateau is characterized by an Arctic heath dominated by *Cladina stellaris*. On the slopes, *Betula glandulosa, Alnus viridis* ssp. *crispa* and *Salix* spp. occur, while *P. glauca, Betula papyrifera* and *Populus tremuloides* are found along the rivers. Finally, in sheltered places, there are fens and peat bogs with *Rhododendron groenlandicum*.

The second ecoclimatic region associated with Whapmagoostui is the low subarctic (CCELC 1989). This continental vegetation in Whapmagoostui is denser, with 5-25 % of overlap and trees that have a maximum height of nine meters (Ducruc 1976). Trees are larger and grow with more density than in the previously described ecoclimatic region. Scott (1995) has mentioned that this ecosystem is continuous throughout the landscape due to the absence of fire and well-drained lichen woodlands. There are four community types: typical lichen-spruce woodlands (*Cladina* spp., *Betula glandulosa* and *Rhododendron groenlandicum*); spruce-moss woodlands (*Larix laricina, Vaccinium* spp., *Betula* sp., *Salix* spp., *Picea mariana, Sphagnum* spp.); open tamarack wetlands (*Sphagnum* spp.-bog, *Larix laricina*-fen) and other typical community types (*Betula papyrifera* and *Populus balsamifera* on the riverside). The wooden heath has *Picea mariana* in the west of its area and vanishes when *Pinus banksiana* and *Kalmia angustifolia* disappear (Ducruc 1976).

Mistissini is a continental area associated with a humid mid-boreal forest and productivity (CCELC 1989). *Picea glauca, Abies balsamea, Betula papyrifera, Populus tremuloides* and *Pinus banksiana* are located in the drier areas, while *Picea mariana* and *Abies balsamea* are in the wet areas and *Larix laricina* is located in the cold sites. Larsen (1980) has previously described the boreal forest, while Blondeau (2003) has updated the types

of species tested. The continental vegetation at Whapmagoostui has many species in common with the boreal ecosystem of Mistissini.

Like Arctic plants, both coastal and continental plants in the subarctic and boreal forests are adapted to their environment and influenced by the climate. Along the coast of Whapmagoostui, the climate is close to the Arctic, with violent winds coming from the bay, low temperatures (as low as -23C°) and annual precipitation averaging 500-700mm (Barger 1971; CCELC 1989). Despite these harsh conditions, the high moisture can be propitious to arboreal growth (CCELC 1989; Scott 1995). Inland, the temperature increases farthe r from the coast and, furthermore, a gradient of rainfall changes the vegetation formations (Hydro-Québec 1993a). Winter is very cold (-23C°) and snowy. On the other hand, while the inland region is subjected to a warmer climate in summer and a colder winter the plants from Mistissini grow faster than in Whapmagoostui (Scott 1995). The modification of plant morphology, genetic variability, physiology and reproduction are related to different natural pressures, such as a short-growing period, low nutrient levels in the soil, low temperature, wind and low light intensity. In both areas, the plants have to grow faster, make molecules for photosynthesis and other primary and secondary metabolism and stock food reserves (Savile 1972).

Cree of Eeyou Istchee Elders and Healers of Mistissini and Whapmagoostui are surrounded by similar plant species from the boreal forest, as well as different plant species from the coastal Arctic area in the northern community. TM provided from the surrounding regions and the natural resources available in this environment are arguably influenced to a great extent by the characteristics of this ecosystem.

2.3. Oxidative stress

Oxidative stress occurs as a result of free radical production, particularly in the absence of antioxidant defenses (McCord 1985; Young *et al.* 1992). Environmental and genetic influences increase the oxidative stresses production, and therefore T2D and related complications (Baynes 1991; Maxwell 1995).

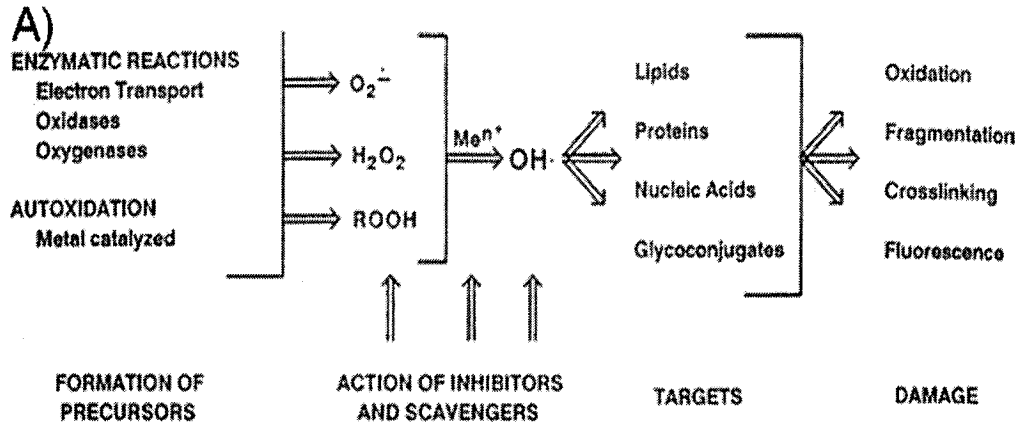
Oxygen is used by all aerobic living organisms, but during metabolism may lead to the formation of highly reactive free radicals (Figure 1A; Dalton 1995). The free radicals found most frequently are the ROS such as superoxide, hydroxyl radical, aqueous peroxyl radical, singlet oxygen, ozone, nitrogen oxide and nitroxide radical (Halliwell 1997; Skeaff 2002). Excited by abnormal electron numbers (Fig. 1B), they are extremely reactive and play a destructive role. For example, in pancreas β-cells, they induce an imbalance in the production of insulin, which may provoke hyperglycaemia (Grankvist *et al.* 1979; Godin *et al.* 1988; Larson 1988; Oberley 1988; Maxwell 1995).

Cerami *et al.* (1988) describe free radicals produced through oxidation and glycation processes. Therefore, glycoxidation products are formed in biological systems. This oxygen toxicity creates fatty acid imbalances or lipid metabolism and may encourage the development of T2D symptoms (Baynes 1991; Terao *et al.* 1992; Young *et al.* 2000). Indeed, in T2D patients, cells are exposed to oxidative stress (Petlevski *et al.* 2003). Oxidation, which is also a key mechanism involved in the deterioration of stored food (Su *et al.* 1986), modifies cellular membranes (Dix and Aikens 1993; Haslam 1996). A variant of oxidation is lipid peroxidation, another oxidative stress linked to T2D because it causes cellular malfunction such as involving cells implicated in the insulin pathway (Baynes 1991) or endothelial cells implicated in artherosclerosis (Duvall 2005). This cardiovascular disease is the major factor responsible for morbidity and death in people with T2D (Scheffer *et al.* 2005). Lipid peroxidation implicates low-density-lipoproteins (LDL) that aid in the transport of cholesterol in the blood to peripheral cells (Fruchart 1992). The oxidation of LDL causes foam cells to form with macrophages (Esterbauer *et al.* 1992) and it plays a role in artherosclerosis development, which has been well explained by Duvall (2005), as well as others who have explained the mechanism (Dix and Aikens 1993; Kalyanaraman 1995; Barakat *et al.* 1996). It has also been shown that LDL derived from patients with T2D is significantly more susceptible to oxidation from ROS than LDL derived from normoglycemic controls (Levy *et al.* 2000). Thus, lipid oxidation of LDL, artherosclerosis and T2D are interconnected due to oxidative stress, and also due to glycation products. Indeed, the product of glucose auto-oxidation as an oxidant, causes glycoxidation which damages the conformation of the apolipoprotein

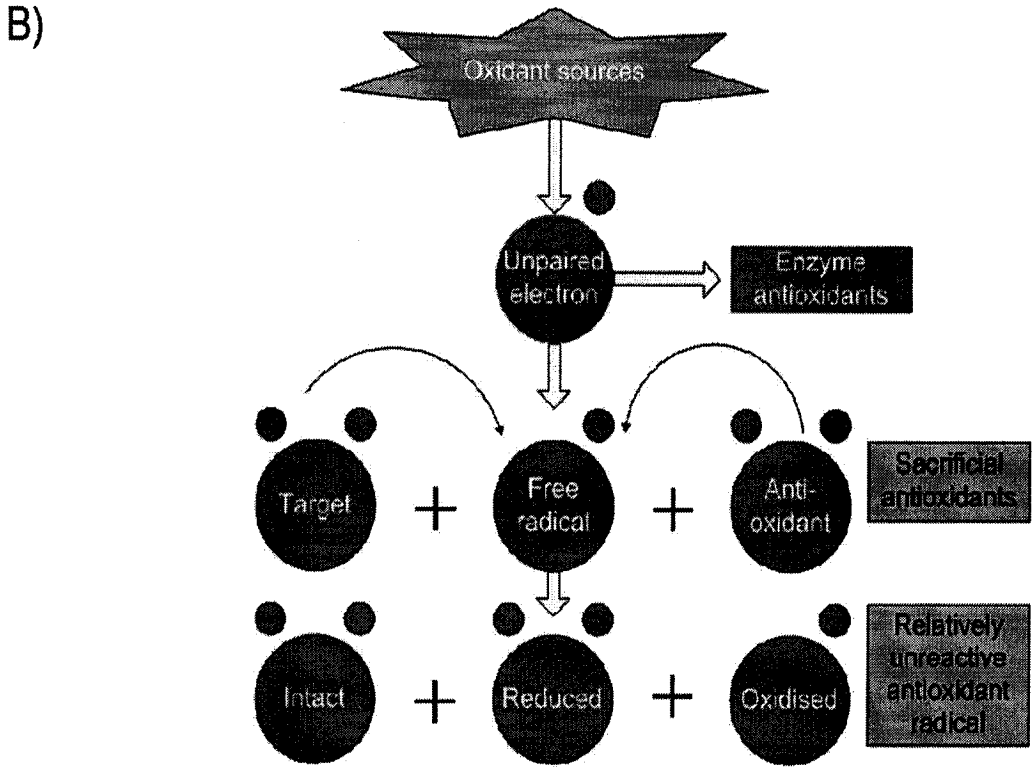
leading to lipid peroxidation and to the development of late complications of diabetes (Baynes 1991). In other words, in a situation where there is hyperglycaemia, diabetics are submitted to high amounts of glucose autoxidation glycation. There is an increase of ROS, which induces the peroxidation of LDL and finally leads to eventual cell damage (Hunt *et al.* 1990).

The secondary aspect of oxidative stress is the absence of antioxidant defenses, since during metabolism antioxidants capture protons against lipid peroxidation. In the absence of antioxidants, free radicals cannot be detoxified (Johns 1990). Natural antioxidants that combat oxidative stress could be endogenous or exogenous (Baynes 1991; Dalton 1995; Johns 1999; Huang *et al.* 2005). Considered as inhibitors (illustrated in Fig. 1), enzymes such as glutathione peroxidase, glutathione reductase, superoxide dismutase and peroxidase are endogenous antioxidants (Godin *et al.* 1988), being produced during metabolism (Thompson and Godin 1995). However, they exist at low levels in the blood of diabetics (Oberley 1988; Giugliano *et al.* 1995).

Secondary metabolites isolated from plant parts such as wood, bark, stems, leaves, fruits, roots, flowers, pollen and seeds, may have antioxidant properties (Pratt 1992). Since oxidative stress has been shown to have a link with complications associated with diabetes and artherosclerosis, exogenous antioxidants, which help resist oxidative stress damage, may prevent symptoms and development of T2D (Bailey and Day 1989; Douillet *et al.* 1998; Baynes and Thorpe 1999; Farvid *et al.* 2005).



Baynes (1991, p.406) Copyright © 1991 American Diabetes Association



Adapted from Maxwell (1995, p.350) Copyright © 1995 Adis

Figure 1.

A) Oxidative stresses from environmental and genetic factors follow this general pathway and may contribute to the development of the complications associated with T2D. It is shown by enzymatic and nonenzymatic sources resulting from the formation of intermediate precursors (superoxides, hydrogen peroxides and lipid peroxides) that conduct to reactive species accumulation (hydrogen radicals). Inhibitors (enzymes) decrease the accumulation of precursors. Radical scavengers, water and lipid soluble antioxidants such as vitamins, limit the hydrogen radical damage on biological molecules (targets). An excessive production of free radicals causes damage to cells and tissues.

B) The pathway is represented by an unbalanced free radical that could be reduced in the presence of antioxidants or enzymes and limit target deterioration.

2.4. Plant antioxidants

Pratt (1992) and Skeaff (2002) have described the functions of natural antioxidants as reducing agents of free radicals, ROS, radical-scavengers with metals (Niki *et al.* 1995), or as quenchers of the formation of singlet oxygen (Halliwell 1997). They suppress lipid peroxidation (Baynes 1991; Terao *et al.* 1992) and inhibit the oxidation rate (Maxwell 1995). For example, the pancreas β-cells, a target, is maintained intact while the antioxidant is oxidized (Fig. 1B).

It is estimated that among the 250,000 higher plants, >25,000 terpenoids, >12,000 alkaloids, >8,000 phenolics have been isolated (Schutles 1978; Buchanan *et al.* 2000). Less than 1 % of plants species have been studied in phytochemistry and pharmacology (Oubré *et al.* 1997), and even less in relation to their ethnobotany (Cox and Balick 1994). One of the primary studies in antioxidation properties of plants was made by Morreu and Dufraise (Blanck 1955). Pratt (1992) mentioned 500 plants that are known to have antioxidant properties.

These plants and extracted compounds could potentially be used to treat, improve or possibly prevent diseases such as cancer (Jain *et al.* 1999) or diabetes (Marles and Farnsworth 1995). Indeed, some studies have shown antidiabetic properties among traditional medicinal plants (McCune and Johns 2002; Li *et al.* 2004). Also, these plants have phytochemical constituents that may reduce hypoglycaemia (Schultes 1978; Perl 1987) and have also antioxidant properties to treat T2D symptoms (Bailey and Day 1989; Marles and Farnsworth 1995). For instance, TM found among First Nations people in Canada has shown to demonstrate potential antioxidant capacity (McCune 1999). However, the antioxidants found in the TM of the Cree of Eeyou Istchee that have been used to treat T2D symptoms, and the relationship to their medicinal properties, remain relatively unknown.

Through diverse evolutionary mechanisms, plants have acquired a varied array of chemical compounds, some of which possess antioxidant potential (Ehrlich and Raven 1964; Berenbaum 1983; McCune 1999). In the plant, antioxidants may be produced to

suppress the free radicals which are formed as a result of metabolic processes such as photosynthesis, respiration and defense responses (Foyer *et al.* 1994; Dalton 1995). Among many plant-derived antioxidants used in foods and beverages, the most important include flavonoids, flavonols, flavones, cathecins, flavonones, as well as cinnamic acid derivatives, coumarins, phenolic acids, tannins, and finally vitamins like α-tocopherol and ascorbic acid and possibly β-carotene (Larson 1988; Terao 1989; Okuda *et al.* 1992; Pratt 1992; Young *et al.* 1992; Dalton 1995; Niki *et al.* 1995; Thompson and Godin 1995; Haslam 1996; Rock *et al.* 1996; Halliwell 1997; Cowan 1999; Packer and Colman 1999; Skeaff 2002).

An example of exogenous antioxidants from plants is vitamin C, chemically known as ascorbic acid. It has been used in many studies as a reference (Esterbauer *et al.* 1989; Acuna *et al.* 2002; Yen and Hsieh 2002) because it is a prominent plasma antioxidant and is the major water-soluble antioxidant acting as the first defence against free radicals (Larson 1988; Niki *et al.* 1995). For instance, it scavenges hydrogen peroxide (Foyer *et al.* 1994) and protects LDL against copper induced oxidation (Mathiesen *et al.* 1996a, b). It is found in lower quantities in diabetics than in non-diabetics (Som *et al.* 1981; Fruchart 1992; Thompson and Godin 1995). Moreover, vitamin C is known to improve insulin action, because it regenerates α-tocopherol *in vitro* from its oxidized form (Cunningham 1998).

Furthermore, another well-known antioxidant is vitamin E, of which α-tocopherol as the most biologically active form plays a role in the prevention and therapy of human disease (Tucker and Townsend 2005). This lipid-soluble molecule is known for its protective role in β-cells and glucose levels by increasing the production of the amino acid glutathione. Vitamin E is a mixture of γ- and α-tocopherols (Perl 1987; Salonen *et al.* 1995; Thompson and Godin 1995). Among the eight stereoisomers, α-tocopherol is the most abundant lipophilic antioxidant and RRR-α-tocopherol is known to have the highest biological activity (Niki *et al.* 1995; Vaya *et al.* 1997). The combination with phenolic compounds is synergic (Larson 1988). Thompson (1993) has described some of the problems and benefits associated with antinutrients such as phenolics. In diabetic patients,

vitamin E is low in plasma (Salonen *et al.* 1995; Facchini *et al.* 2000). This micronutrient is high in plants, prevents lipid peroxidation, and is therefore useful in the prevention and treatment of diabetes (Gokkusu *et al.* 2001).

Both vitamins C and E are frequently used for *in vitro* studies because they have the ability to quench the ROS responsible for lipid peroxidation (Babiy *et al.* 1990; Jiagal *et al.* 1990; Rifici and Khachadurian 1993). Chemical studies in which people with T2D were administered these vitamins as supplements had a decrease in oxidative stress and better diabetes control (Douillet *et al.* 1998; Farvid *et al.* 2005). However in high doses, antioxidant could interact with cell molecules and potentially disturbe the antioxidant/prooxidant balance (Opara 2002).

2.5. Bioassays and compositional assays

Antioxidant activity can be measured with a variety of assays (Huang *et al.* 2005). There are, for example, assays that evaluate free radical scavenging ability, such as 1,1-diphenyl-2-pycryl-hydrozyl (DPPH), or those that measure lipid peroxidation such as conjugated dienes (CD) and thiobarbituric acid reactive substances (TBARS). Other experiments can measure phenolic content in extracts. The Folin-Ciocalteau colorimetric, for example, is a compositional analysis of phenolics. These are used widely due to their simplicity, effectiveness, and also because they have the ability to accommodate many samples in a short time. They are also popular due to their validity and their sensitivity (Singleton and Rossi 1965; Singleton 1985; Esterbauer *et al.* 1989; Cotelle *et al.* 1996; Sobal *et al.* 2000; Llesuy *et al.* 2001; Sanchez-Moreno 2002). These bioassays and this compositional analysis have been used in measuring the antioxidant activity of plants extracts (Mathiesen *et al.* 1995; Choi *et al.* 2002; McCune and Johns 2002; Owen and Johns 2002; Cai *et al.* 2004; Katsube *et al.* 2004).

Elaborated by Blois (1958), the DPPH assay measures free radical scavenging ability. DPPH is a stable radical molecule used to examine the free radical scavenging ability of compounds *in vitro* by reacting with hydrogen donors. It is used as a screening tool by displaying the plant extracts's non-specific hydrogen atom (or electron) donating activities (Kirby and Schmidt 1997) and odd electrons shown by a strong absorption band

at 517 nm (Ursini *et al.* 1994). For example, DPPH can be used for an initial screening of flavonoid reactivity (Ursini *et al.* 1994; Cotelle *et al.* 1996) and the scavenging activity of certain polyphenols (Okuda *et al.* 1992). In solution, the delocalised electron pair by DPPH is responsible for the characteristic purple colour of the solution. The capacity to donate electrons from plant-derived antioxidants is observed by a loss of the initial purple color of the remaining DPPH radical to a yellow mixture, where the antioxidant radicals contribute to the formation of a stable molecule by quenching the energy of free radicals (Blois 1958; Benvenuti *et al.* 2004). In this reaction, the DPPH molecule acquires a hydrogen atom from the reducing agents, the antioxidants. The assay is found to work well with cysteine, glutathione or ascorbic acid (Blois 1958).

There are also various assays estimating lipid peroxidation, such as CD and TBARS assays. There are also various assays estimating lipid peroxidation, such as CD and TBARS assays, in which human LDL is involved since the latter play a role in the oxidative stress (Esterbauer *et al.* 1990) linked to diabetes (Hunt *et al.* 1990; Desmarchelier *et al.* 1999; Manonmani *et al.* 2005). When free radicals are not scavenged, lipid peroxidation can be initiated and intermediate products are formed. The oxidized apolipoprotein can release conjugated dienes created by the formation of bridges between amino acids, or liberate oxidation bioproducts, which include malondialdehyde (MDA) in 90 % of TBARS (Esterbauer *et al.* 1987; Esterbauer *et al.* 1992).

Specifically, the CD assay, based on continuously monitoring of the oxidation of LDL, measures the increased absorption of CDs, which are oxidation products, at 234 nm. The absorbance vs. time relationship demonstrates three phases: lag time, where there is little or no lipid peroxidation indicated by CD formation; propagation phase, where there is a rapid increase in oxidation products, and a terminal phase where CDs reach a maximum value indicated by a plateau (Esterbauer *et al.* 1989). Results are expressed as the time where the propagation phase is initiated. Esterbauer *et al.* (1989) has called this time the lag time. Antioxidant sources, such as vitamin C and E, will increase lag time, since they inhibit the formation of oxidative products on LDL (Esterbauer *et al.* 1989; 1990; 1991 and 1992).

An additional lipid peroxidation measurement in biological systems including LDL often used with CD assays is the TBARS assay. It measures TBARS production expressed in MDA. The concentrations of TBARS, or the end products, are then measured among end points. The production of TBARS by using the MDA is indirectly proportional to the antioxidant activity. Esterbauer *et al.* (1990) have proven that the lag time in conjugated dienes is correlated with TBARS and lipid hydroperoxides with $r = 0.99$.

Finally, the Folin-Ciocalteau compositional analysis measures phenolic content (flavonoids, tannins, phenolic acids), which are dominant antioxidant components in plants (Proteggente *et al.* 2003). The compositional assay is known for its many qualities, including the presence of colour, less variation, better recovery, being rapid and simple and there is no precipitation. The quantitative method depends on the oxidation of phenolics by a yellow complex formed from phosphomolybdic and phosphotungstic heteropoly acids. It oxidises phenolates, reducing the heteropoly acids to form blue pigments (Singleton and Rossi 1965).

3.0. Rationale, objectives and hypothesis

Despite the emergence of a growing epidemic of T2D among the Cree of Eeyou Istchee, information about Cree traditional medicine at Whapmagoostui, compared with other Cree communities such as Misitssini, as well as the antidiabetic properties in antioxidants of those plant species, is still largely unknown. More work must be done in collaboration with the Cree of Eeyou Istchee in order to promote their traditional knowledge of healing and medicine, as well as finding a way of preventing further cases of T2D.

The overall objective of the thesis was to identify and compare traditional antidiabetic medicine among different Cree communities and evaluate their antioxidant values. First, this was done by interviewing Elders and Healers in order to know plants used by the Cree of Whapmagoostui for treating symptoms related to T2D. Quantitative ethnobotanical techniques were used to fully understand the data and then to compare it to the one obtained from a previous ethnobotanical study done in Mistissini and to the one extirpated from the scientific literature. Finally, based upon the information described in the first manuscript, the antioxidant potential of plants was addressed using different *in vitro* bio-assays. Water-soluble total phenolic content of extracts of medicinal plants used by the Cree of Eeyou Istchee in both communities, as well as the content of the extracts of non-medicinal plants, were measured. A ranking method evaluated the importance of each plant along the three antioxidant bioassays. The Spearman's correlation test attempted to correlate Cree knowledge with antioxidant abundance found in the TM used. Therefore, based on SIV and the ranking values on TM, a preliminary list of potential prioritized antidiabetic plants could be chosen for further *in vitro* and *in vivo* analysis and clinical trials.

The hypotheses of this study are that despite changes in Cree traditional knowledge and practice, Elders and Healers have conserved TM successfully by continuing to use plants with antidiabetic properties for treatment of T2D symptoms. Furthermore, the TM used by two Cree communities in Québec is homogenous, and both the TM used by these communities is based on the use of certain plants with antioxidants in abundance that can be used in the treatment of T2D.

4.0. Introduction to Manuscript I

Considering the increasing problem of T2D among people of the Cree community (Hegele *et al.* 2003) a collaborative project, based on asserting the validity of traditional knowledge, was created to examine plants with antidiabetic properties still used by Elders and Healers of the Cree of Eeyou Istchee in order to prevent disease expansion. Leduc *et al.* (2006) have studied eighteen medicinal plants used by Cree of Eeyou Istchee in the southern community of Mistissini in relation to Cree specific-literature. This manuscript expands upon previous work and ethnobotanical studies in order to evaluate traditional medicine used by Cree Elders and Healers of the more northern community of Whapmagoostui. Also, based on quantitative ethnobotany, this preliminary study compares the data collected with those from Mistissini and with the literature. This ethnobotanical study and research proposes to identify the potential of certain plant species as well as to prioritize them with the aim of validating TM and encouraging more dialogue and research on the benefits of antioxidants in TM.

5.0. Manuscript I

Ethnobotanical investigation of plants used for the treatment of Type 2 Diabetes by two Cree Eeyou Istchee communities (Québec, Canada):
Quantitative comparisons and evaluation.

Fraser, M.-H., Johns, T., Cuerrier, A.

Abstract

The Cree Eeyou Istchee (CEI) has been particularly affected by Type 2 Diabetes (T2D), with a prevalence of 17.7 %. A recent study of the CEI of Mistissini explored traditional medicine (TM) for the treatment of T2D and its complications by means of a quantitative ethnobotanical approach. In the present study, we expanded our ethnobotanical survey on the CEI of Whapmagoostui to identify TM, to rank the plant species used for TM and then to use these results as a basis for a comparison between the two communities and the data assessed from six previous studies focusing on the Cree in Canada. Interviews were undertaken to determine which plant species are used to treat a predetermined list of fifteen symptoms associated with T2D. A combined total of 26 medicinal species were identified by a total of 65 interviews with Cree Elders and Healers. *Rhododendron groenlandicum, R. tomentosum* and *Larix laricina,* as well as five other species encompassing Pinaceae and Ericaceae, were the most cited plant species and have been prioritized for *in vitro* and *in vivo* analysis. This preliminary ethnobotanical study illustrated a strong degree of TM conservation and homogeneity of knowledge among different Cree communities found in Québec and in the rest of Canada. It provides a framework for research directed at the eventual prevention of T2D among the Cree. Further experiments could be initiated to determine the medicinal activity of plant species used by CEI to validate TM in relation to T2D treatment.

Keywords: Cree Eeyou Istchee; Diabetes; Quantitative ethnobotany; Medicinal plants.

5.1. Introduction

In recent decades, Type 2 Diabetes (T2D) has become an enormous health problem in the world with 171 million cases (World Health Organization 2005). The problem of diabetes is widespread among Indigenous communities in Canada (Delisle *et al.*1993), such as the Cree Nation (Zieba 1992; Thouez *et al.*1990), and more specifically in the Cree Eeyou Istchee (CEI) communities (Robinson 1988; Brassard 1991 and Brassard *et al.* 1993; Dannenbaum *et al.*1999; CBHSS 2001). CEI, with a prevalence of 17.7 %, are more affected by this chronic disease than the Canadian population which has a 4.8 % prevalence (Légaré 2004). The extent of the problem among the Cree is illustrated by a doubling of T2D over the past fifteen years (Brassard *et al.* 1993). Modernization of lifestyle over several decades has exposed this population to factors inducing T2D. Environmental and genetic factors also increase the development of this chronic disease: change in lifestyle, lack of physical activity, nutrient deficiencies, socio-economic stresses and the *thrifty genotype* (Neel 1962; Young *et al.* 2000; Hegele *et al.* 2003). Western European influences in diet have also contributed to the rise and increase in cardiovascular diseases and obesity among aboriginal populations (Young and Sevenhuysen 1989; Brassard and Robinson 1995).

The Cree Nation is widespread throughout Canada (East Cree Language 2005). CEI is a subpopulation of the Cree Nation, and one of the eleven First Nations in Québec. They count for a population of 14,600 divided into nine different communities, situated between the 49th and 55th parallel along the James and Hudson Bay (Fig. 1) (*Secrétariat aux affaires autochthones* 2005). Situated approximately 1,200 kilometres from Montréal, Whapmagoostui (56.17°N, 77.45°W) is one of five Cree coastal communities, the others being Waskaganish, Eastmain, Wemindji and Chisasibi. Mistissini is one of the four continental communities, including Waswanipi, Oujé-Bougoumou and Nemaska. With no road access due to its northeast location, Whapmagoostui differs from Mistissini in being dependent on planes and boats for transportation (Adelson 1992).

The Cree have different dialects (Cree Cultural Institute 2005) and ecoclimatic regions (CCELC 1989; Hydro-Québec 1993a; Robinson *et al.* 1995; Scott 1995). Indeed,

Whapmagoostui is part of the hemiarctic coastal ecosystem in the southern part of the Hudson Bay and, further inland, of the boreal forest, whereas Mistissini is situated further south within the 300 000 km^2 of Québec boreal forest. A greater diversity of plant species is present in Whapmagoostui in comparison with Mistissini, due to the arctic species located in the hemiarctic area (Deshaye and Morisset 1985). An inventory by Forest and Legault (1977) listed 488 taxa in comparison with 453 species around Mistassini Lake (Blondeau 2003). Among other differences between these communities there is a decrease in T2D rates corresponding with latitude in which 14.1 % of Mistissini population and 6.3 % of Whapmagoostui population are affected (CBHSS 2001).

Despite dietary intervention strategies and conventional programs for diabetes prevention, T2D is still increasing among the CEI (Boston *et al.* 1997; Gray-Donald *et al.* 2000). This is due to the lack of sensitivity in prevention strategies that do not take into consideration cultural differences and diversity among the population (Boston *et al.* 1997). It has been shown that alternatives to this lack of success involve working in conjunction with traditional approaches to health, such as traditional medicine (TM) using plants species. This can potentially facilitate the involvement of the population (Bailey and Day 1989; Marles and Farnsworth 1995; Oubré *et al.* 1997; Young *et al.* 2000). Some studies document the utilisation of medicinal plants among Cree in Canada (Holmes 1884; Strath 1903; Beardsley 1941; Leighton 1985; Dominique *et al.* 1985; Marshall *et al.*1989; Zieba 1992; Siegfried 1994). In Québec, it is known that Cree Elders and Healers still use plant-based medicines (Adelson 1992).

Based on the traditional approach, a primary long-term project was initiated in Mistissini in 2003 by Leduc *et al* (2006). With the participation of Elders and Healers, this ethnobotanical study documented eighteen medicinal plants that treat fifteen T2D symptoms and results were compared to Cree-specific literature using quantitative ethnobotany. Since there are few ethnobotanical studies completed with the participation of the Cree people in Québec (Blacksmith 1981; Leduc *et al.* 2006) and an increasing rate of T2D among CEI, it becomes important to expand our understanding of TM in relation with T2D by doing further ethnobotanical studies. For example, no study related to T2D

symptoms has been done with the community of Whapmagoostui, despite its unique geographical context as a coastal rather than inland community. In addition, although some research has used quantitative methods in the analysis of ethnobotanical data (Johns *et al.* 1990 and 1994; Phillips and Gentry 1993a, b), few studies have compared TM among groups of Indigenous people using a quantitative approach (Prance *et al.* 1987; Moerman 1996; Höft *et al.* 1999). Moreover, with the exception of Leduc *et al.* (2006), there have not been any ethnobotanical surveys and studies comparing medicinal plants quantitatively and their use among Cree communities in Québec.

Considering the importance of reducing the rates of T2D, this study aims to explore the use of TM by the Cree people in Whapmagoostui to treat symptoms related to this illness, as well as examine the order of importance of species used. Furthermore, it aims to prioritize the potential antidiabetic species for further *in vitro* and *in vivo* analyses and compare the list of plant species stemming from the CEI communities of Whapmagoostui and Mistissini and also those found in Cree-specific literature based on six references by using quantitative ethnobotanical techniques. It is expected that TM is an important aspect of Cree culture that has been preserved over time, and would therefore be homogenous amongst the communities situated in similar geographical contexts, particularly those inhabiting the boreal forest.

5.2. Materials and methods

5.2.1. Study site

Whapmagoostui and the Inuit community of Kuujjuaraapik are separate communities comprised within the same settlement (Adelson 1992). It has a population of 793 with an average age of 22.7 years (Statistic Canada 2003; Secrétariat aux affaires autochtones 2005). Between 1996 and 2001, the village experienced an increase of 24.6 % in population (Statistic Canada 2003). Adelson (1992) calculated that 39 % of women and 36 % of men born from 1940 to 1960 still practiced traditional activities. Three different languages are used, which are Cree, English and French. The basic services in the community today include a health clinic, school, grocery store, post office and police

station. Health services are administrated and organized by the Cree Board of Health and Social Services (CBHSS).

Whapmagoostui was chosen as the project site because of several factors. First, this community differs geographically from the southern community of Mistissini, situated inland. Indeed, Whapmagoostui, the northest village, is situated along a coastal environment (Fig. 1). There is also a specific flora found in those regions, which include the ecoclimatic regions of hemiarctic and boreal forests (Fig. 1). In addition, Whapmagoostui has potentially a population of Elders and Healers knowledgeable in the use of TM (Adelson 1992).

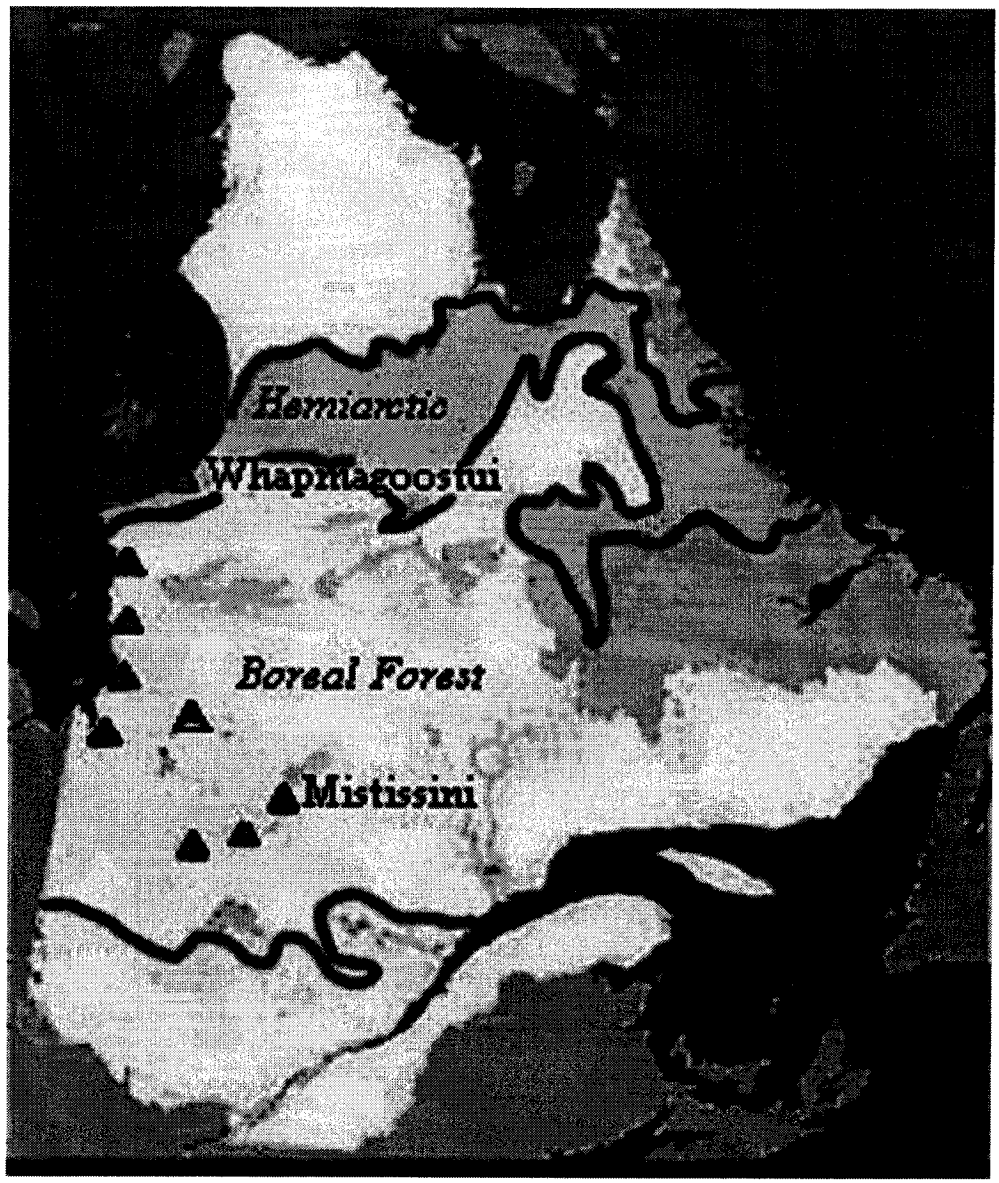
5.2.2. Ethical approach

Based on ethical rules proposed by Scott and Receveur (1995), this project was first explained to Robbie Dick (Chief of Elders and Healers) and a group of Elders and Healers. We also sought and received the consent of David Masty (Chief of Whapmagoostui) and the CBHSS in order to perform fieldwork in Whapmagoostui. Furthermore ethical guidelines established by McGill University were signed before beginning fieldwork (Appendix 2). Feedback information was given in person to the participants and to the community during the summer of 2005.

5.2.3. Interviews

In order to explain the project to the community and the Elders and Healers, a preliminary visit to Whapmagoostui was undertaken. This allowed researchers to become familiar with the community and their culture and to facilitate communication and establish a relationship (Spradley 1979; Lipp 1989; Bobbish and Magonet 1990; Freeman 1992; Alexiades 1996). Reaffirmation and validation of the role of TM was presented to Elders and Healers as an important element of the research (Marles 2001).

The Cree residents of Whapmagoostui participated on a voluntary basis and the help of an interpreter was sought during the interviews. Elders or Healers were consulted at their homes in a familiar environment, where the aim of the interviewers was to increase comfort in discussing TM in the context of this project. The interviews were scheduled on



Adapted from *Secrétariat aux affaires autochthones* (2005)
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Figure 1.

Repartition of the CEI communities, Québec, Canada (Δ). Located in the hemiarctic region, Whapmagoostui is the most northern community, while Mistissini is situated in the boreal forest.

the basis of the participant's willingness and availability (Spradley 1979; Lipp 1989; Kuhnlein 2000). The confidentiality of each participant was explained clearly to them, with a number system assigned to each Elder or Healer before the interview (Martin 2004). The student and the interpreter explained the aims of the project to participants, as well as introducing its collaborators and the logistics of the interview. Following Adelson (1992), each participant signed the consent form approved by the ethics committee (Appendix 2). Interviews were performed with individuals or with the members of one family. This was done to avoid confusion or mistakes made by individuals, and particularly because some families could have their own traditional preparation or secret medicinal plant species (Lipp 1989).

In order to have comparable results, the method developed by Leduc *et al.* (2006) was applied; this included a questionnaire that asked about the plants species used and the symptoms of T2D they were used for, if applicable. Also, the type of interview used was similar to the previous study. Two types of interviews were performed, one that was semi-structured and one that was unstructured (Kemp and Ellen 1984; Alexiades 1996; Cunningham 2001). The semi-structured interview included a questionnaire (Appendix 3), which paid careful attention to plant names, remedies or treatments, as well as the plant parts used (Kale and Kale 2002). Following Leduc *et al.* (2006), Elders and Healers were questioned regarding T2D and the definitions of what encompassed 'being healthy' in their particular context. But most of the interviews were about medicinal plants related to the symptomatology of T2D, according to fifteen symptoms based on clinicians and diabetes specialists (Oubré *et al.*, 1997; McCune and Johns 2002, 2003). The plant species were shown to the participants to confirm the identification of the medicinal plants. The unstructured interview entailed evaluation of the name of a maximum number of plants collected around the community, as well as their medicinal properties. This type of interview optimized the collection of information (Burgess 1982). Both semi-structured and unstructured interviews were recorded (Olympus DS-2000).

All materials and notes, such as linguistic transcription by interpreters, were verified and revised with the help of the informant. The same procedure was applied to the plant samples for analysis (Lipp 1989).

5.2.4. Plant acquisition

Both medicinal plant and non-medicinal plant samples were collected based on the ethnobotanical methods of Lipp (1989), Cox and Balick (1994), Oubré *et al.* (1997), Cunningham (2001), Marles (2001), Parabia and Reddy (2002) and Martin (2004) with the following modifications. First, the selection of localities, time of harvesting and which species and/or population of plants species to collect were assessed with the help of the informants before starting the fieldwork. If any rare species were mentioned by participants, the conservation of the plant population was taken into account on ethical grounds and in respect to ancestral rights. Second, the collection and identification of plant species was done with the participants. Plants were identified by their scientific name, their Cree name(s) and their vernacular name. Each species was photographed in their environment with a Nikon COOLPIX5400. The exact location of plant collection was noted using a Global Positioning System (GPS Garmin Etrex vista). Then, 500 grams of fresh material were collected for further laboratory analysis. Four voucher specimens were made for each medicinal species and kept at the Marie-Victorin Herbarium (*Jardin Botanique de Montréal*; MT), at *Aanischaaukamikw* (Cree Cultural Institute) and at the community school in Eeyou Istchee of Whapmagoostui.

5.2.5. Quantitative ethnobotany

In the present report, different quantitative and statistical tools were used on the ethnobotanical set of data from three sources: for Whapmagoostui, Mistissini and the Cree specific-literature. Quantitative ethnobotany was done by using numerical taxonomy (Mantel 1967; Sneath and Sokal 1973; Lapointe and Legendre 1990, 1991, 1995; Cuerrier *et al.* 1990, 1998; Legendre *et al.* 1994; Legendre and Legendre 1998; Podani 2000; Dutilleul *et al.* 2000). These techniques were used with the aim to classify and/or cluster objects or specimens (Podani 2000), such as taxa based on their character states.

To describe the traditional knowledge in Cree medicine, matrices were used. Matrices are the basic element for quantitative ethnobotanical analysis and provide fieldwork information from participants by telling which TM is associated with fifteen T2D symptoms based on the frequency of mentions. In order to rank TM and prioritize species for further analyses, the Syndromic Importance Value (SIV) is calculated based on the importance of TM mentioned for the fifteen T2D symptoms, the degree of its use, and the corresponding knowledge from Elders and Healers. The SIV is used to determine which plant is most likely to have antidiabetic compounds. To compare results stemming from a given set of data, several analyses are performed. The Spearman's correlation test was performed with SIV results ranked accordingly from each set of data. Mantel and Podani permutation tests were performed on different matrices to compare the similarity of set of data information. In other words, homogeneity of traditional knowledge was compared based on raw or similar matrices. Also, cluster analysis (CA) was performed to describe any relationship among medicinal plants and the T2D symptoms. The dendrogram that was generated produced clusters of medicinal plants that treat similar symptoms. Finally, dendrograms generated from the CA, using data from Whapmagoostui, Mistissini and Cree-specific literature, were compared using the consensus test (CT). This test demonstrates the similarity of dendrograms. Numerical taxonomy analyses were performed with SPSS version 11.0, Prologiciel R 4.0d6 and Permute 3.4 α 8 software.

5.2.5.1. Matrices

A matrix of fifteen symptoms of T2D and all medicinal plants was generated from the ethnobotanical data. Two other matrices were created with the ethnobotanical data of Mistissini provided from 34 informants (Leduc *et al.* 2006) and Cree-specific literature to enable comparisons. Using methods derived, modified and adapted from Leduc *et al.* (2006), the Cree literature matrix was based on six references; Holmes (1884), Strath (1903), Leighton (1985), Marshall *et al.* (1989), Zieba (1992) and Siegfried (1994). The resulting matrix, however, differs from Leduc *et al.* (2006) by dismissing *Vaccinium vitis-idaea* and *Vaccinium angustifolium* due to zero frequency in the literature previously used in the matrix (15 X 15). The information is based on 71 participants, when each reference is considered separately and counted as being provided by a separate informant, when the

source did not stipulate how many informants were interviewed. Otherwise we recorded the number of informants if it was mentioned.

5.2.5.2. Syndromic Importance Value

The calculation of the Syndromic Importance Value followed the methods developed by Leduc *et al.* (2006). The mathematical formula displayed below assesses whether or not the plant species is commonly used in the treatment of T2D symptoms. The formula used is:

$$SIV = ((\Sigma w_i S_i / 15) + (\Sigma w_i F_i / N*15)) / 2$$

$$SIV = ((\Sigma w_i S_i) + (\Sigma w_i F_i / N)) / 2$$

w = weight of symptom

S = symptom mentioned (1) or not mentioned (0)

F = frequency of mentions

N = number of persons interviewed

For each fifteen symptoms, 'w' is a number between 0 and 1, where $\Sigma w = 1$. This variable allows for the prioritization of symptoms based on the strength of their association with T2D. This weight was determined by experts in the field of clinical diabetes and diabetes research to whom we asked to rank all symptoms in regards to T2D (Leduc *et al.* 2006). Symptom 'S' is either 1, if the plant species was mentioned for treatment of the symptom, or 0 if the plant species was not mentioned, where the maximum $\Sigma S = 15$ symptoms. Frequency of mentions 'F' were compiled, the number of persons interviewed 'N' at Whapmagoostui was 31. Overall, SIV was calculated for each medicinal plant found at Whapmagoostui. The SIV was also used to rank medicinal plant species identified from Mistissini in 2003 and mentioned in the Cree-specific literature, in order to be comparable in a correlation test.

5.2.5.3. Spearman's coefficient of rank correlation

The Spearman's correlation test verifies the correlation between two sets of data (Sokal and Rohlf 1962). Plant species were placed in decreasing order of SIV. If species were ranked similarly in both sets, the correlation would equal 1.

5.2.5.4. Permutation tests

Mantel and Podani permutation tests were performed using different matrices (Mantel 1967; Leduc *et al.* 2006). Both tests compare matrices conveying the data from

Whapmagoostui, Mistissini and the Cree-specific literature surveys. The Mantel test statistically compares symmetric matrices. Different coefficients were used: Euclidean distance (D1), simple matching (S1), Jaccard (S7) and Steinhaus (S17), as described in Legendre and Legendre (1998). They were applied to the raw matrices before being used in the Mantel test. Euclidean distance and Steinhaus are applied with the quantitative matrix, while simple matching and Jaccard are used with a binary matrix (presence/absence). The latter matrices were created because many references in the literature omitted the total number of participants interviewed in relation to medicinal species. Therefore, medicinal species were simply mentioned in association with the disease. Symmetrical coefficients, such as simple matching and Euclidian distance, take into account double-zeros. In numerical taxonomy the species will be considered close, because they share similar information. Jaccard and Steinhaus, asymmetrical coefficients, exclude double-zeros. Permutations of the symmetrix matrices were applied to species. Columns and rows were simultaneously permuted 10,000 times in any possible arrangement or ordering. The second method, the Podani algorithm, was elaborated by Podani (see Leduc *et al.* 2006) based on a direct calculation from the raw matrix without applying any coefficient of distance or similarity. Again, 10,000 permutations were used. Although not used in our study, the Podani algorithm can also permute rows or columns individually. From both tests, the null hypothesis can be read as follow: the two matrices being compared are no more similar than randomized matrices.

5.2.5.5. Cluster analysis

From the methods of Sokal and Rohlf (1962) and of Podani (2000), cluster analyses were performed on medicinal species using the Whapmagoostui data. In the present study, Operational Taxonomic Units (OTUs) were species. Simple matching (which includes double-zeros) and Jaccard (which excludes double-zero) coefficients were applied to the raw matrix of Whapmagoostui in order to verify the impact of the absence and presence of double-zeros on the different dendrograms. Hierarchical group analyses were done using the single linkage algorithm. The aim behind the use of cluster analyses (CA) was that species within genus or genus within a family would be grouped together due to similar phytochemical constituents.

5.2.5.6. Consensus tests

Consensus tests (CT), as carried out by Cuerrier *et al.* (1990, 1998) and developed by Lapointe and Legendre (1990) were applied. Dendrograms were compared using the ultrametric matrices, which are also called cophenetic matrices (Sokal and Rohlf 1962; Lapointe and Legendre 1991 and 1995). This is a matrix in which its values convey the information to form the dendrogram. CT used a double permutation procedure (Lapointe and Legendre 1990, 1991; Legendre *et al.* 1994). Coefficients (Euclidean distance, simple matching, Jaccard and Steinhaus) were applied to the raw matrices to obtain a symmetric matrix. The cophenetic matrices, that represent the dendrograms, were obtained through CA. All comparisons were based on 10,000 permutations. The algorithm proceeds by randomization of the three different dendrogram properties; topology-shape, scale-fusion level and leaf position (Sneath and Sokal 1973). Then, fixed fusion levels forced the levels to reach the same values as in the actual dendrogram. The randomization of the cophenetic matrix is obtained by randomizing the fusion level positions, and not the values. The null hypothesis stipulates that two dendrograms are no more similar than randomized dendrograms.

5.3. Results

5.3.1. Fieldwork

Of the 31 Elders and Healers interviewed in 24 households, thirteen had T2D. The age of the informants ranged from 53 to 90 years, with an average of 70 years. During the course of the present study, 75 species were shown to the participants. This includes 54 non-medicinal plants thriving near Whapmagoostui (Appendix 4). The length of interview varied from 30 to 180 minutes. Altogether, informants indicated a total of 674 mentions in regards to the fifteen symptoms.

5.3.1.1. Ethnobotanical data

Table 1 shows twenty-one species from nine families that are used to treat T2D symptoms in Whapmagoostui. Many of these medicinal plant species fall into the Pinaceae and Ericaceae plant families. All trees from the area were found to be used for TM. Because of unclear information from participants, six plant species were rejected (Table 2).

However, a total of 26 different TM used among CEI are able to treat T2D symptoms. These include six additional medicinal plants in comparison with Mistissini including the following: *Cladonia rangiferina, Empetrum nigrum, Juniperus communis, Leymus mollis, Sphagnum fuscum* and *Rhododendron tomentosum.*

A few plant species such as *Juniperus communis, Kalmia angustifolia, Larix laricina, Picea glauca, P. mariana, Rhododendron groenlandicum, R. tomentosum* and *Sorbus decora* treat more than nine symptoms (Table 2). Back/kidney pain and infections are the symptoms treated most frequently by Elders and Healers. Rheumatism/arthritis and problems with appetite are symptoms found to be treated less frequently by participants. More than ten species treat headache, back/kidney pain and heart/chest pain. Certain plant organs, such as spruce needles, are used more frequently than other plant organs, such as the gum and cones of spruce. The medicine is prepared with simple preparation such as by decoction, infusion and poultices, for which plant tissue is scraped, crushed or reduced into powder form. In both communities, Elders and Healers used mostly cambium (six plant species) and leaves (five plant species) but rarely bark, gum, needles or root (two plant species for each tissue). In Whapmagoostui, Elders and Healers used several tissues from specific TMs (juniper and mountain ash), whereas at Mistissini they primarily use one organ.

In addition, it was found that Cree names have different pronunciation between the two communities. For example, *Larix laricina* is called "Waachinaakin" at Whapmagoostui (Table 1) and "Watnagan" at Mistissini (Leduc *et al.* 2006). Also, certain TM used in Whapmagoostui have been found to have several different names (see *Pinus banksiana*). While this did not affect the overall results of the present project, discovering differences in traditional names added a new dimension of factors that had to be considered during the study.

Nine of the medicinal species used in Whapmagoostui are common with the ones used in Mistissini. Nevertheless, both communities have their own specific species that treat particular symptoms. Four and five species used in Whapmagoostui and Mistissini,

respectively, represent remedies unique to each community (Table 2). Blurred vision is treated exclusively with *Abies balsamea* (Mist.) and *Vaccinium vitis-idaea* (Whap.). Also, in Mistissini, infections are treated with two other trees, *Abies balsamea* and *Alnus incana* ssp. *rugosa.* Many Elders and Healers in Whapmagoostui treat weakness/arthritis but less than three participants from Mistissini treat this T2D symptom. In the northern village, they used the smoke of *Sphagnum fuscum* and *Leymus mollis* for that T2D complication. Finally, *Sphagnum fuscum* is used in Whapmagoostui as a compress to relieve backpain.

On the other hand, eleven medicinal plants used in Whapmagoostui are listed in the literature for the same symptoms. The raw data gathered in Whapmagoostui showed both differences and similarities between this set of data. *Salix planifolia* was widely mentioned in the six references, whereas *Kalmis angustifolia* has been much more cited by the Elders and Healers of the studied community. However, both sets of data showed similar frequency for *Rhododendron groenlandicum* and *Pinus banksiana.* Also, participants said that all forms of pain had vast flora remedies while many different medicinal plants found in the literature treat symptoms for weakness/arthritis. Nevertheless, TMs treat most infections among both groups.

5.3.1.2. Ranking species

Figure 2 illustrates SIV values, whereas Table 3 lists the ranking order according to the SIV of the medicinal species used in both communities and those recorded in the ethnobotanical literature. SIVs were calculated for a total of twenty-one plant species altogether (fifteen for Whapmagoostui and Mistissini and sixteen for the literature). The highest SIV is represented by *Rhododendron groenlandicum* and *Larix laricina* which are the most cited TM to treat T2D symptoms in both communities. The literature presented the highest SIV for *Abies balsamea.*

Comparable SIVs can be found for *Juniperus communis* and *Salix planifolia* between Whapmagoostui and the literature, whereas seven common species to Mistissini and the literature shared the same SIVs. *Pinus banksiana* has almost the same SIV and rank among the three groups. Also, the SIV of medicinal plants from Whapmagoostui are higher than the ones from the two other species groups. This is due to the total record of

specific mentions that influence the calculation of the SIV. Indeed, the 31 participants in Whapmagoostui cited a total of 674 mentions between plants species and symptoms, in comparison to 129 mentions for Mistissini.

As shown in Table 3, the ranks of five plants species used in the literature and Whapmagoostui are very similar (*Rhododendron groenlandicum, R. tomentosum, Sorbus decora, Pinus banksiana* and *Empetrum nigrum*), whereas the ranks of *Rhododendron groenlandicum, Larix laricina, Picea mariana* and *Vaccinium vitis-idaea* in both communities were similar.

5.3.2. Ethnobotanical survey

5.3.2.1. Spearman's coefficient of rank correlation

This test compared the ranking of medicinal plants based on SIV among Whapmagoostui, Mistissini and the Cree-specific-literature obtained in Table 3 (Fig. 3). Positive correlations are found in every comparison, with the one involving Whapmagoostui and the Cree-specific literature showing the highest correlation ($r = 0.773$; Fig. 3b). The lowest correlation is found between both Cree communities. This was influenced by *Picea glauca,* which ranked fourth and fourteenth in the northern and southern communities, respectively (Table 3; Fig. 3c).

5.3.2.2. Permutation tests

Table 4 shows the coefficient of correlation (r) and level of significance (p) from permutation tests on matrices of the three sets of data. Mantel and Podani permutation tests show significant similarity in 7 out of 15 cases. The significance is stronger with Podani than with the Mantel permutation test. For example, matrices highly similar were Mistissini and Cree-specific-literature illustrated with a significance of $p = < 0.0001$ in Podani test. Within the Mantel test, simple matching and Jaccard coefficients have shown stronger similarity when Whapmagoostui and literature matrices were compared. Therefore, the binary matrix (presence/absence) demonstrated more similarity than the raw quantitative matrices from which they were generated.

5.3.2.3. Cluster analysis

Figure 4 shows dendrograms indicating the relationships among the fifteen medicinal plants used in Whapmagoostui based on T2D symptoms. To verify the data in more depth, different coefficients based upon the presence and absence of the double-zero, were applied. Also, by removing frequency of mentions and including double-zero in the raw matrix, two distinct grades were formed in dendrogram *a*, with seven and eight species, respectively. The first grade tends to group members of the same families or even of the same genus. In the other grade, six other families are represented and form an artificial grouping. *Pinus banksiana* and *Vaccinium vitis-idaea* are present in the second grade due to a high number of double-zeros which they share with the other plant species within that grade. Therefore, in this grade, the species treat fewer symptoms.

In dendrogram *b*, double-zeros were excluded in the binary raw matrix. Only shared symptoms are taken into consideration in the calculation of the coefficient. Although the Pinaceae and Ericaceae retain the same position, the structure changed somewhat with other families in comparison with dendrogram *a*. Except for a small grade made of the four first species, no other grade is formed and the dendrogram has a comb-like morphology. *Salix planifolia* and *Kalmia angustifolia* have changed position.

5.3.2.4. Consensus test

Table 4 illustrates the results from the CT analyses comparing dendrograms (see Fig. 5). Only 3 out of 15 tests show significant similarities between dendrograms. Therefore, dendrograms would be deemed to be dissimilar. The stronger significance was with Jaccard coefficient ($p = 0.0001$). Also, the results demonstrated that excluding double-zeros (Steinhaus and Jaccard) give better significance than the Euclidean distance.

Figure 5 illustrates some of the dendrograms being compared between CEI communities and the literature based solely on the Jaccard coefficient. Dendrograms *a* and *b*, for Whapmagoostui and Cree-specific literature, show similarities among dendrogram proprieties. Excluding double-zeros, the same groups of plant species are clustered in both dendrograms for which they treat the same T2D symptoms. Similarity between dendrogram *a* and *b* is not repeated when dendrograms *c* and *d* or *e* and *f* are compared. Therefore, dendrograms have different morphologies, leaf positions and fusion levels.

Table 1. Plants used in Whapmagoostui to treat the fifteen symptoms associated with diabetes.

Medicinal plants	Family	Common name[a]	Cree name
Andromeda polifolia L. ssp. *glaucophylla* (Link) Hultén	Ericaceae	Bog rosemary	Kakouboushk
Branch	---	---	NA
Cladonia rangiferina (L.) Nyl.	Lichenophyta	Gray reindeer lichen	Whapskumuk / Epshatuk
Dead tree (stump)	---	---	Kiskischatuk
Empetrum nigrum L.	Empetraceae	Crowberry	Ebshjimend
Juniperus communis L.	Cupressaceae	Common juniper	Kakachiumi-nathikw
Kalmia angustifolia L.	Ericaceae	Sheep laurel	Uschipikwh
Larix laricina (Ru Roi) K. Koch.	Pinaceae	Tamarack	Waachinaakin
Leymus mollis Trin.	Poaceae	American dunegrass	Kawabash / Houskwav
Picea glauca (Moench) Voss	Pinaceae	White spruce	Menihikwu
Picea mariana (Mill.) BSP.	Pinaceae	Black spruce	Eeatuk
Pinus banksiana Lamb.	Pinaceae	Jack Pine	Wischisk / Iyashick / Ivashick / Eiacht
Rhododendron groenlandicum (Oeder) Kron et Judd	Ericaceae	Labrador tea	Wiisichabikwu
Rhododendron tomentosum (Stokes) Harmaja ssp. *subarcticum* (Harmaja) G. Wallace	Ericaceae	Small Labrador tea	Wesigibuks
Salix glauca ssp. *callicarpaea* (Trautv.) Böcher	Salicaceae	Beautiful willow	Hostibegontuck
Salix planifolia Pursh ssp. *planifolia*	Salicaceae	Flatleaf willow	Waskayabaduk
Sphagnum fuscum (Schimp.) Klinggr.	Sphagnaceae	Moss	Awasistche
Sorbus decora C.K.Schneid.	Rosaceae	Mountain ash	Miskoomishee
Thuja occidentalis L.	Pinaceae	White cedar	NA
Vaccinium uliginosum L. var. *alpinum* Bigel.	Ericaceae	Alpine bilberry	N'chiminatuk
Vaccinium vitis-idaea L. var *minus* Lodd.	Ericaceae	Partridge cranberry	Wiisichiminh
TOTAL : twenty-one species	nine families		

[a] Common name taken in Blondeau and Roy (2004)

Table 2. Medicinal plants used in Mistissini and Whapmagoostui.

Species	Part used [a]	Symptoms [b]	Set of data [c]
Abies balsamea (L.) Mill.	Ca	5	M
Alnus incana ssp. *rugosa* (Du Roi) R.T. Clausen	Ca	4	M
Andromeda polifolia L. ssp. *glaucophylla* (Link) Hultén [d]	A	M	W
Branch [d]	S	G, J, K	W
Cladonia rangiferina (L.) Wigg. (lichen)	A	K	W
Dead tree [d]	A	Healing	W
Empetrum nigrum L.	Be	N	W, L
Gaultheria hispidula (L.) Muhl.[e]	Be	1	M
Juniperus communis L.	R, L, S, Be	A, B, F, H, J, K, L, N	W, L
Kalmia angustifolia L.	L,R	A,E,F, G, H, I, J, K, L M, N, O	M, W, L
Larix laricina (Ru Roi) K. Koch.	Ca	No C, N	M, W, L
Leymus mollis Trin.	A	A, H, L, M	W
Lycopodium clavatum L.	A	2	M
Picea glauca (Moench) Voss	Co, Ca, N, S, G	A,B,C,E,F,D,H,I, J,K,L,O,M	M, W, L
Picea mariana (Mill.) BSP.	Co,N,S, G	A,B,C,D,E,F,G, HI,J,K,L,M,O	M, W, L
Pinus banksiana Lamb.	Co	D,E,O	M, W, L
Populus balsamifera L. [d]	Ca	1	M
Rhododendron groenlandicum (Oeder) Kron et Judd	L	A,B,C,D,E,F,G, H,I,J,K,L,MNO	M, W, L
Rhododendron tomentosum (Stokes) Harmaja ssp. *subarcticum* (Harmaja) G. Wallace	L	A,B,C,D,E,F,G, HI,J,K,L,M,O	W, L
Salix glauca ssp. *callicarpaea* (Trautv.) Bocher [d]	L	H,J,L,O	W
Salix planifolia Pursh ssp. *planifolia*	Ba	J,M,G	W, L
Salix spp.	Ca	4	M
Sarracenia purpurea L.	A	2	M
Sphagnum fuscum (Schimp.) Klinggr.	A	A,C,E,H,I,J,K,M ,O	W
Sorbus decora C.K.Schneid.	S, L, Ba, Ca	A,B,C,D,H,J,L, M,N,O	M, W, L

Table 2. *Continued.* Medicinal plants used at Mistissini and Whapmagoostui.

Species	Part used [a]	Symptoms [b]	Set of data [c]
Stereocaulon paschale (L.) Hoffm. [d]	A	1	M
Thuja occidentalis [d]	L	J,K,G	W
Typha latifolia L. [d]	R	1	M
Vaccinium angustifolium Aiton	Be, R	2	M
Vaccinium uliginosum L. var. *alpinum* Bigel. [d]	R	1	M, W
Vaccinium vitis-idaea L. var *minus* Lodd.	Be	C,G,N	W
TOTAL: 26 species	45 organs		18M, 21W

[a] Abbreviations of part used: all (A); bark (Ba); berries (Be); cambium-inner bark (Ca); cone (Co); gum (G); leaf (L); needle (N); stem (S); root (R).

[b] *Numbers*: Total T2D symptoms treated (Leduc *et al.* 2006).
Abbreviations of T2D symptoms treated: A- Headache; B-Thirst; C- Blurred vision; D-Appetite; E- Sores/Wounds (foot); F- Diarrhoea; G-Abscesses/toothache/boils; H-Back/kidney pain; I- Rheumatism/arthritis; J-Infections; K- Inflammation; L- Heart/Chest pain; M- Fainting/weakness (including anaemia); N- Urinary/diuretic; O- Sore or swollen limbs.

[c] Mistissini (M) (Leduc *et al.* 2006); Whapmagoostui (W) and Cree literature (L).

[d] Excluded from analysis, due to the ambiguity of answers from the Elders and Healers.

[e] Only leaves were collected as fresh material.

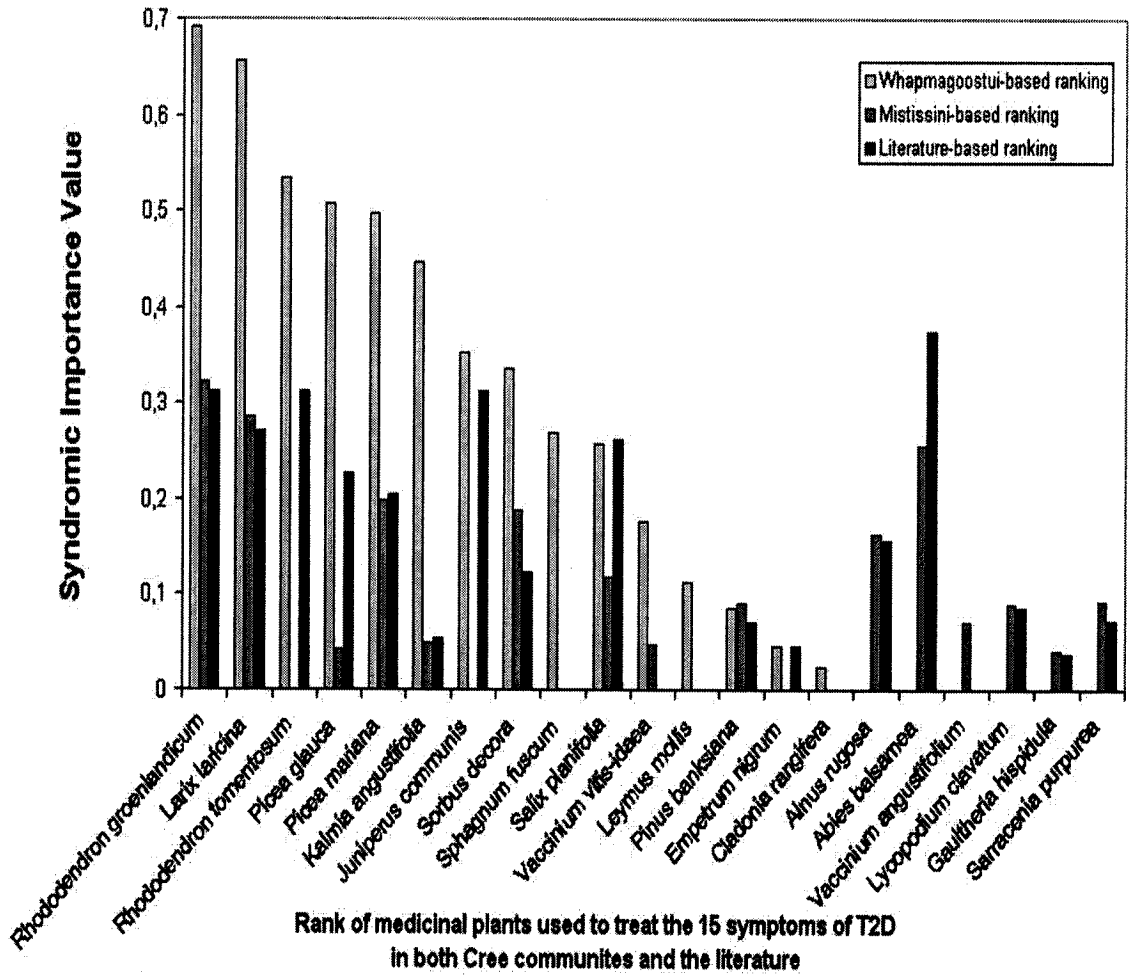

Figure 2.

Syndromic Importance Value (SIV) for the medicinal plants mentioned in Mistissini (Leduc *et al.* 2006), Whapmagoostui and from the Cree-specific literature. SIV takes into account the frequency of record, the weight of each symptom and the number of symptoms for which the plant has been mentioned.

Table 3. Ranking order according to the Syndromic Importance Value of each species.

Medicinal plant species	Whapmagoostui	Mistissini	Literature
Rhododendron groenlandicum	1	1	2
Larix laricina	2	2	5
Rhododendron tomentosum	3	0	3
Picea glauca	4	14	7
Picea mariana	5	4	8
Kalmia angustifolia	6	12	14
Juniperus communis	7	0	4
Sorbus decora	8	5	10
Sphagnum fuscum	9	0	0
Salix planifolia	10	7	6
Vaccinium vitis-idaea	11	13	0
Leymus mollis	12	0	0
Pinus banksiana	13	9	13
Empetrum nigrum	14	0	15
Cladonia rangiferina	15	0	0
Alnus incana ssp. *rugosa*	0	6	9
Abies balsamea	0	3	1
Vaccinium angustifolium	0	11	0
Lycopodium clavatum	0	10	11
Gaultheria hispidula	0	15	16
Sarracenia purpurea	0	8	12
TOTAL: 21 species	15 species	15 species	16 species

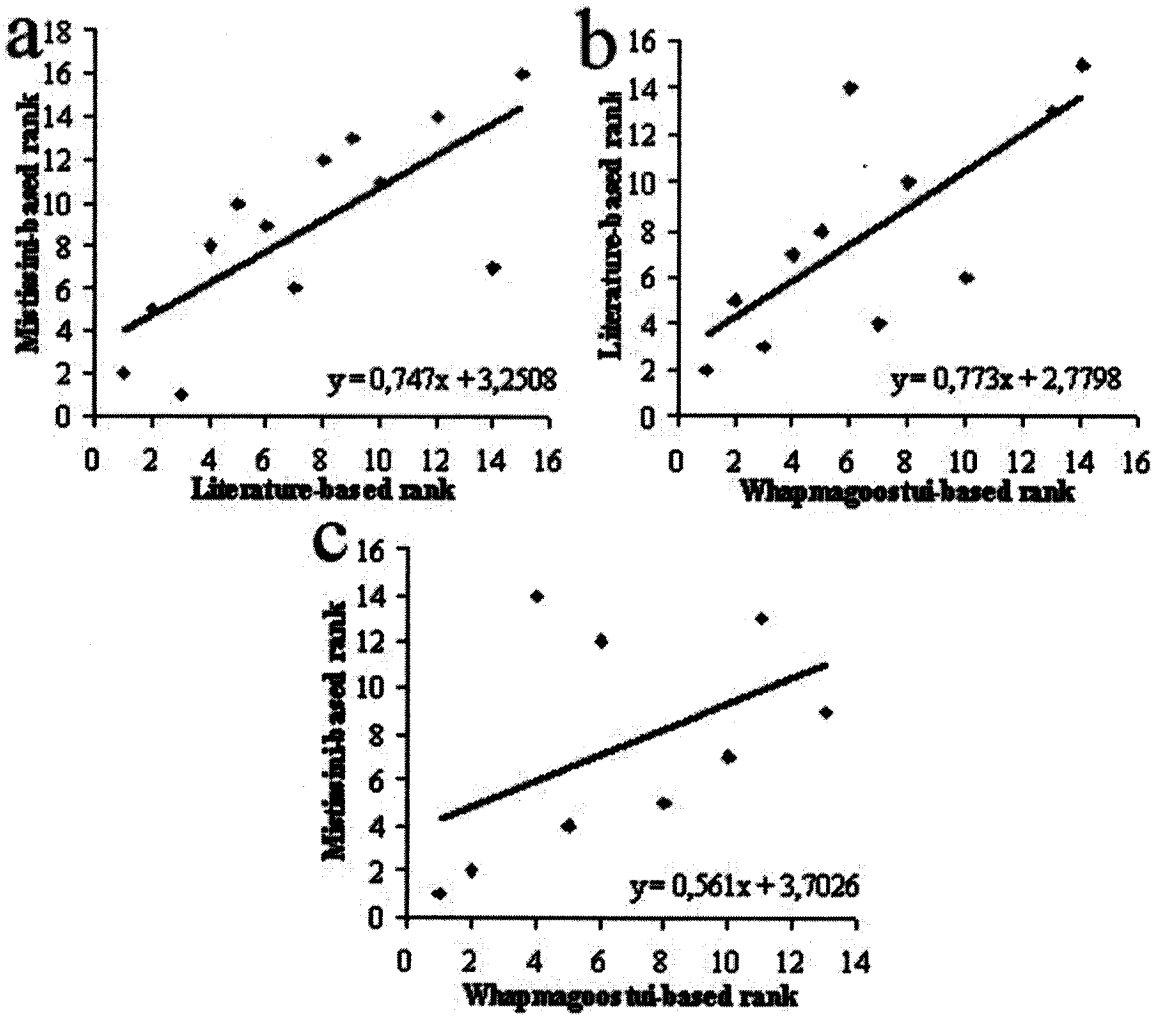

Figure 3.

Regression analysis and Spearman correlation coefficient (*r*) of medicinal plants, based on SIV. Linear regressions between a) Literature and Mistissini (r = 0.747) b) Literature and Whapmagoostui (r = 0.773) and c) Mistissini and Whapmagoostui (r = 0.561).

Table 4. Results from Mantel and Podani permutation tests based on matrix comparisons and from consensus tests (CT) based on dendrogram comparisons according to Mistissini, Whapmagoostui and the data from Cree-specific literature data.

	Coefficients [a]	Whapmagoostui Literature (15 X 11)	Whapmagoostui Mistissini (15 X 9)	Mistissini Literature (15 X 13)
Mantel	Euclidean distance D1	0.1374 / 0.2065	0.2021 / 0.1347	0.0816 / 0.3459
	Sheinhaus S17	0.541 / 0.0209 *	0.2015 / 0.203	0.1793 / 0.0875
	Jaccard S7	0.7734/ 0.0012 **	0.2935 / 0.1464	0.2319 / 0.0686
	Simple matching S1	0.4733/ 0.0026 **	-0.2464/ 0.0578	0.2773 / 0.0328 *
Podani	Manhattan distance (p)	0.0099 **	0.0223 *	<0.0001 *** [b]
Consensus test	Euclidean distance D1	0.001 / 0.831	0.0317 / 0.3510	0.0208 / 0.321
	Sheinhaus S17	0.3541/ 0.0038 **	0.0813 / 0.1605	0.0015 / 0.7916
	Jaccard S7	0.6469/0.0001***	0.1163 / 0.0957	0.0013 / 0.7801
	Simple matching S1	0.1701 / 0.0204*	0.0584 / 0.1553	0.0532 / 0.0615

[a] Mode Q with coefficient of correlation (*r*) / level of significance (p)

[b] Leduc *et al.* (2006).

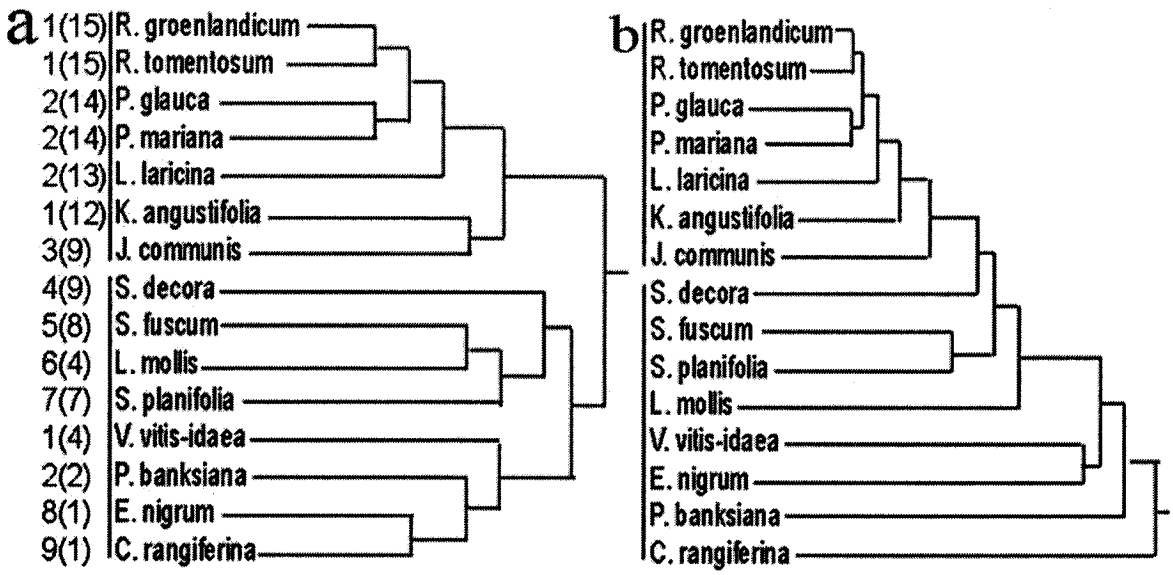

Figure 4.

Dendrograms of the fifteen medicinal species used in Whapmagoostui in relation to T2D symptoms. Clustered species treat the same T2D symptoms. The upper cluster shows phylogenetic relationships except for *Pinus banksiana* and *Vaccinium vitis-idaea,* which are parts of the lower cluster. The fifteen plant species are indicated with its family in both dendrograms 1 = Ericaceae; 2 = Pinaceae; 3 = Cupressaceae; 4 = Rosaceae; 5 = Sphagnaceae; 6 = Poaceae; 7 = Salicaceae; 8 = Empretraceae; 9 = Lichenophyta. Information in parenthesis indicates the total number of symptoms treated for those fifteen TMs. Single linkage dendrograms are based on a) simple matching coefficient and b) Jaccard coefficient.

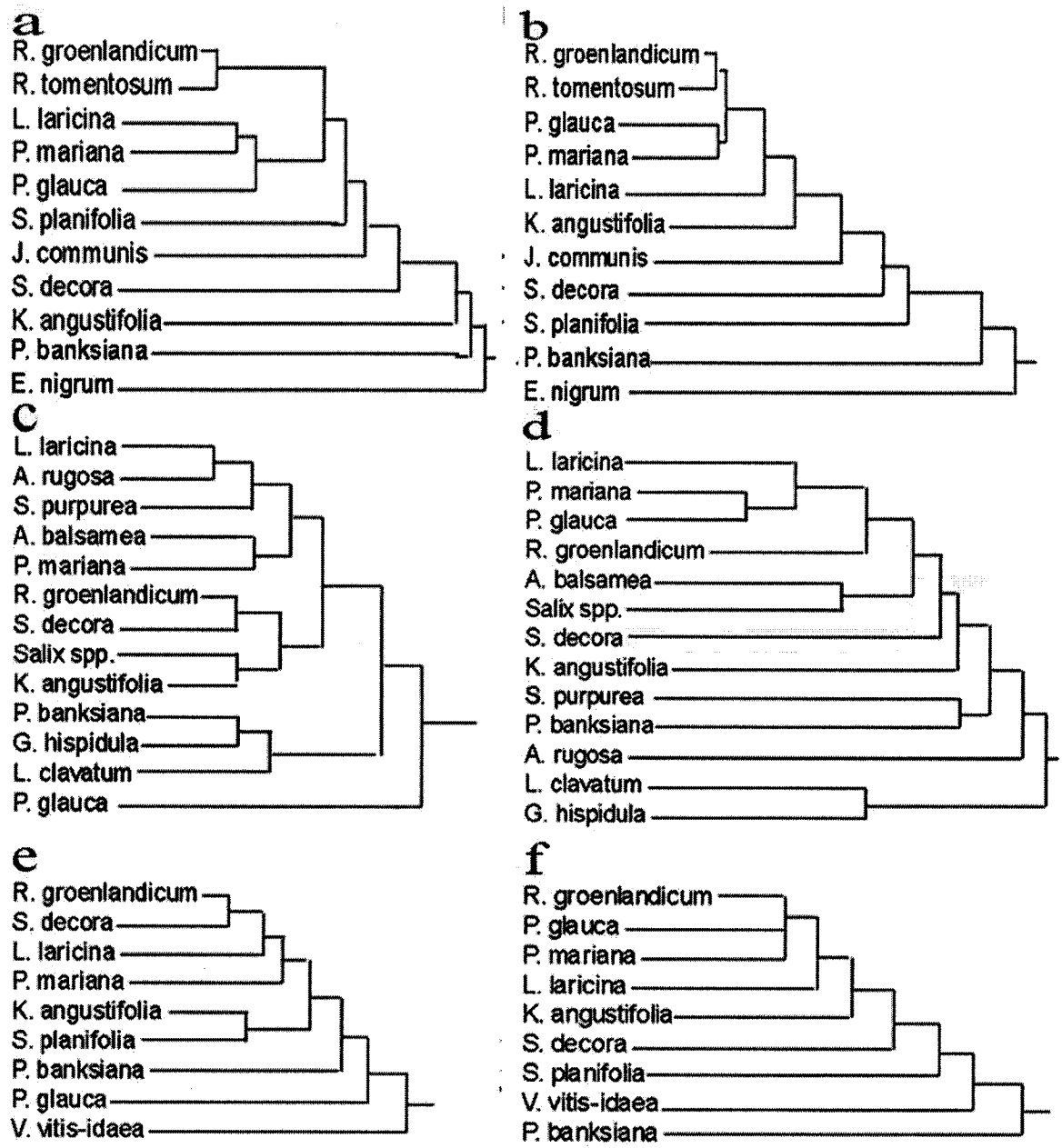

Figure 5.

Dendrograms based upon the use of medicinal plants to treat T2D symptoms for a) Cree-specific literature (11 species); b) Whapmagoostui (11 species); c) Mistissini (13 species); and d) Cree-specific literature (13 species); e) Mistissini (9 species); and f) Whapmagoostui (9 species). They were obtained using single linkage with a Jaccard coefficient.

5.4. Discussion

5.4.1. Ethnobotanical survey and species ranking

5.4.1.1. Whapmagoostui traditional medicine

The ethnobotanical information, gathered through the survey done in Whapmagoostui added new data and complemented the surveys realised in Mistissini in 2003 and in the existing literature concerning the Cree in Canada. As expected, Elders and Healers of Whapmagoostui have preserved TM. Twenty-one medicinal species are used in Whapmagoostui to treat T2D symptoms, including three new TMs: *Cladonia rangiferina, Leymus mollis* and *Sphagnum fuscum*. Also three plant species were not mentioned in Mistissini but were mentioned in Whapmagoostui, which include the following: *Empetrum nigrum, Juniperus communis* and *Rhododendron tomentosum.*

The present project is the second study that has calculated the ranking of TM based on the SIV results, previously elaborated by Leduc *et al.* (2006). Ranking of the species, based on the ethnobotanical data of Whapmagoostui and the quantitative results, yielded a suggested prioritized list of eight species for further *in vivo* experiments. The top three species widely used by all 31 Elders and Healers were *Rhododendron groenlandicum, R. tomentosum* and *Larix laricina*, for which the highest SIV and ranks were obtained. These are also widespread in the boreal forest (Forest and Legault 1977) which suggests that the Cree users of TM select common species in their environment. Specifically, they select common Pinaceae and Ericaceae, also considered frequent species of the boreal forest. In Whapmagoostui, the landscape is composed of 69.1 % of boreal plant species, including those plant families (Deshaye and Cayouette 1988). Furthermore, additional boreal plant species such as *Kalmia angustifolia, Picea glauca, P. mariana.* and *Juniperus communis* could be give high importance since they treat more than nine symptoms (Table 2), and presented the next highest SIV (Fig. 2) and therefore have a high rank (Table 3). If importance is given to high consent among informants, *Vaccinium vitis-idaea,* an Ericaceae mentioned to treat blurred vision (71 %), could be also prioritized.

McCune and Johns (2003) have shown the importance of some specific medicinal plants in treating symptoms of T2D based on the use of plants by Indigenous peoples living within the Canadian boreal forest. In the present study, among the prioritized TM, similar species as in the previous study stand out, specifically those that treat more than six symptoms such as *Juniperus communis, Rhododendron groenlandicum* and *Picea mariana*. These species also have antioxidant activity in relation to T2D symptoms (McCune and Johns 2002), which supports the importance of considering them for further research.

These eight plants mentioned above have medicinal particularities and are also commonly used by many people of First Nations background (Holmes 1884; Strath 1903; Arnason *et al.*1981; Zieba 1992; Moerman 1998; McCune 1999). Although *Rhododendron groenlandicum* has been listed in this Cree medicine as in the present survey, *R. tomentosum* is less known. According to participants, both species of Labrador teas look the same, with the exception of differences in size. The small Labrador tea is used for children, whereas the common Labrador tea is used for adults. Moreover, the inner bark of tamarack has been mentioned as a Cree TM for back/kidney pain (Arnason *et al.*1981). Since common Labrador tea and tamarack obtained the highest rank from the SIV, they must have beneficial medicinal effects, probably due to their secondary metabolites (Glasby 1991; Arnason et al 1981; Kuhnlein and Turner 1991; Powell and Raffa 1999a, b). Black and white spruces have been also studied for their medicinal proprieties (McCune 1999).

At Whapmagoostui, both spruces were used to treat the same T2D symptoms. Participants stated that the pitcher plant is a very important medicine due to its strong and effective treatment, but has to be taken in moderation due to its potential toxicity. Similarly, sheep laurel has toxic alkaloids and terpenoids (Glasby 1991; Burke *et al.* 1989). In 77 % of cases in Whapmagoostui, juniper treats one of the most highly ranked symptoms shown to be a complication of T2D: urinary tract problems (Leduc *et al.* 2006) as well as partridge cranberry which treat blurred vision (another key T2D symptom).

Cree people within Whapmagoostui have accumulated somewhat different knowledge concerning traditional remedies, as was observed among the Inuit (Cuerrier *et al.* 2005). Indeed, the eight prioritized species have particular distribution influenced by both ecoclimatic regions (boreal and hemiarctic) within the Whapmagoostui area. Therefore, Elders and Healers have acquired dissimilar medicical knowledge due to the geographical availability of the flora, since this depends on their origin: whether inland, coastal and south or north. Even among Crees of similar origin, each family may have their own traditional knowledge (Lipp 1989) influenced by the composition of the environment. For example, in Whapmagoostui, *Picea glauca* grows along the coast in the hemiarctic forest, and *Picea mariana* grows mostly inland (Hydro-Québec 1993a; Farrar 1996), while the majority of the population, who inhabit the coast, use *P. glauca.* But Elders and Healers, who spend most of their lives far from the shore, reportedly use *Picea mariana.* These received 45 and 36 mentions in the raw matrix, respectively. Some participants used both kinds of spruces and differentiate them based on their specific odours. In the same way, more than half of the Elders and Healers interviewed are familiar with *Kalmia angustifolia,* even if it is far from town due to its inland distribution located in the bogs and peaty barrens (University of Connecticut 2006; Elders and Healers, *pers. comm.*). During the fieldwork, it was observed that some Elders and Healers use many plant species, whereas others always use the same species, usually Labrador teas and tamarack for different symptoms. From the ethnobotanical data, the project showed that Elders and Healers in Whapmagoostui have particular traditional knowledge, depending on their origin.

5.4.1.2. Cree medicine in Québec

Based on the survey and the ranking comparison, the study demonstrated that ethnobotanical data from Whapmagoostui has shown different information than that found in Mistissini (Leduc *et al.* 2006). This is due to the geographic locations of both communities and local plant biodiversity within these respective ecoclimatic regions. Elders and Healers, and their choice and use of TM, have been influenced by their origins and also on the vegetation gradient that determines plant availability: from the boreal forest in the south to the hemiarctic forest in the north. Specifically, fieldwork results

demonstrated that there are cultural differences among the Cree, which can be seen in their dialect, knowledge, and utilization of TM and specific emphasis on the use TM.

Medicinal plants used in Whapmagoostui (Table 1) had different names from those used in Mistissini (Leduc *et al.* 2006). This heterogeneity of the dialect among the Cree Nation has also been shown to be paralleled among Inuit communities in Nunavik following an east to west gradient (Dorais 1973, Cuerrier *et al.* 2005). Although Cree knowledge continues to be passed on to new generations (Bobbish and Magonet 1990), the CEI language shows small phonetic differences in the pronunciation among the nine CEI communities (East Cree Language 2005; Jason Coonishish, *pers. comm.*).

Furthermore, ethnobotanical knowledge and the utilization of plant TM between CEI communities revealed dissimilarities. Through traditional practices and story-telling (Bobbish and Magonet 1990; Masty 1998), TM has been transmitted by Cree ancestors along different clans and communities, therefore creating local knowledge differing between CEI communities. Since Whapmagoostui is isolated from the other eight CEI communities, Cree medicine is more preserved here than in the southern community, as Maberley *et al.* (2000) have shown among the Cree of Western James Bay. Indeed, all plant species in common use between Whapmagoostui and Mistissini showed a higher SIV (Fig. 2). Thus, TM was more cited, known and used by Elders and Healers in the north than in the south where participants mentioned them with less frequency. Although the number of participants in both places is almost identical, the Cree of Whapmagoostui mentioned more medicinal functions than the Cree of Mistissini for the same TM.

Zieba (1992) has reported that the adaptation of cultural traits is a result of the specific 'niche', physical, biological and cultural, within which a population is located. Cultural traits are key factors that have been shown to vary significantly amongst Indigenous communities (Kuhnlein and Receveur 1996; Kuhnlein 2000). The comparison between communities could support varied degrees of western influences (Brassard 1991). This is even more of a possible factor when considering other influences, including the presence of an Inuit influence from inhabitants of Kuujjuaraapik who live adjacent to

Whapmagoostui (Honigmann 1952). Although this influence is beyond the scope of the present study, it cannot be overlooked and may explain some of the differences between Whapmagoostui and Mistissini.

Although the results have shown nine similar medicinal plants species used in CEI communities, some of them have been used with varying emphasis. The same plant used in both villages, for example, will be known and used for different purposes. As within the population of Whapmagoostui, we observed different uses for *Picea glauca* between different communities due to its flora distribution, and which is mostly sporadic in the vicinity of Mistissini (Scott 1995). Consequently, it is used with less frequency in the south where only two citations have been made for this species. At Whapmagoostui, 45 mentions of this species have been recorded. It was also shown by both calculated of SIV for *P. glauca* (Fig. 2) and therefore, it was ranked differently (Table 3). Elders and Healers of Mistissini used *Picea glauca* to treat only thirst, whereas in Whapmagoostui white spruce is used to treat fourteen symptoms associated with T2D. Almost all participants used the conifer, a well-known TM among Indigenous people (Arnason *et al.* 1981; Leduc *et al.* 2006) for infections, which is a serious complication of T2D. Another example demonstrates yet another emphasis among Cree medicine in Québec, with the use of *Vaccinium vitis-idaea* that treats blurred vision, particularly in Whapmagoostui (15 out of 21) and urinary problems in Mistissini (only one mention).

The availability of medicinal plants in the environment and their provenance influenced the choices made by Elders and Healers for the Cree medicine in each village studied. Moreover, some species are specific to one place. Although grass-like plants are widespread species in Whapmagoostui, where the two most frequent belong to the Poaceae (9 %) and Cyperaceae (14 %) (Forest and Legault 1977), Moerman (1996) has observed that grasses are traditionally less used than trees. This trend is also observed in the present study, except for *Leymus mollis* used by only one Elder. The American dunegrass is mostly found near the littoral in the hemiarctic ecoclimatic region of Whapmagoostui as well as in Canadian arctic environment (Porsild 1964). Therefore, it is more available for the Elders and Healers than an inland species. *Rhododendron*

tomentosum with a northern repartition is not found around Mistissini (Porsild 1964); therefore it is not used in Cree medicine of that community. Mistissini also has specific medication, such as *Gaultheria hispidula, Sarracenia purpurea* and *Abies balsamea,* which are not found in the northern community. However, these species have been cited for use by Cree in other parts of Canada (Arnason *et al* 1981; Blacksmith 1981; Zieba 1992; McCune 1999). These local species from Whapmagoostui complemented the previous list of the CEI medicine in Mistissini related to the treatment T2D symptoms (Leduc *et al.* 2006). Those specific results showed the importance of studying different communities within the same First Nation or cultural group and in this case the Cree because it provided different medicinal species to identical ailments. Also, results from Whapmagoostui expanded and updated the existing Cree medicine knowledge.

5.4.1.3. Cree medicine in Canada

Within the course of this study, ethnobotanical data and ranking information from Whapmagoostui and the literature demonstrated similarities among eight medicinal species. Three species obtained similar SIV; *Salix planifolia, Juniperus communis* and *Pinus banksiana* and five species showed closed rank (Table 3). As in the studies done among other Cree communities in Canada, the preparation of the Cree medicine is similar. Moreover, back pain and infections are treated in the same manner unlike treatments for other groups (Zieba 1992; Moerman 1998). As well, plant organs or tissue used are similar to those found in the literature, such as the leaf of *Rhododendron groenlandicum* (Arnason *et al.* 1981; Zieba 1992; Moerman 1998; McCune 1999).

5.4.2. Quantitative ethnobotanical tools

This study has shown the importance of using quantitative tools in the analysis of ethnobotanical data. The interpretation of the survey and the ranking is based on the three sets of data; Whapmagoostui, Mistissini and Cree specific-literature. This was done in more depth in order to evaluate and statistically confirm the prevalence of TM use for T2D as well as provide additional insight into the differences between its use in different Cree communities. The quantitative tools, rarely used in ethnobotany, looked for more sophisticated explanations from the ethnobotanical data. As Leduc *et al.* (2006) have

shown, this project demonstrated the applicability of tools that can be used to compare ethnobotanical information within a particular cultural and Indigenous community.

5.4.2.1. Correlation

The different rankings of species are correlated as shown by the Spearman's coefficient of rank correlation (Fig. 3). As expected, based on ethnobotanical data, quantitative ethnobotany demonstrated that the medicinal species used to treat T2D symptoms are the same between the CEI communities studied and across Canada. Comparisons of the data indicated significant correlations, despite geographic isolation and differences in the presence of specific flora. They also show similarities in the importance of each medication used to treat T2D symptoms among the groups compared.

5.4.2.2. Cluster analysis

This analysis illustrates the relationship among plants used for T2D symptoms. In comparison with Leduc *et al.* (2006), the present work has shown a symptoms-based correlation between members of the same plant family. Indeed, dendrograms of medicinal plants in Whapmagoostui showed, whatever the coefficient used, two groups of plants: 1) Ericaceae-Pinaceae, except *Pinus banksiana* and *Vaccinium vitis-idaea,* and 2) a second grade grouping the other eight plants. CA has shown that the shape of the dendrogram is influenced by the number of symptoms treated by each species and, obviously, the double-zeros. For example, regarding Operational Taxonomic Units (OTUs) positions (see Labrador teas, spruces, pitcher plant and juniper), they follow the descending numbers of symptoms treated (Fig. 4). The first grade, including Pinaceae-Ericaceae, was represented by the species that treat more than nine symptoms. Therefore, this reveals similarities in the treatment of T2D symptoms. For example, *Rhododendron* spp. and *Picea* spp. treat the same T2D symptoms. *Juniperus communis,* a Cuppressaceae, is also clustered with *Kalmia angustifolia* indicating common medicinal treatment. The second group of clustered plants was influenced by their double-zeros for which they shared common ones (Figure 4). They are only used to treat a few symptoms.

Several plant species in the second grouping have less than twenty mentions from participants. In the raw matrix, *Empetrum nigrum* and *Cladonia rangiferina* had the same

number of double-zeros and *Leymus mollis* and *Sphagnum fuscum* were reported to be used to treat weakness, chest and back pain. Also, *S. fuscum* and *Salix planifolia* are clustered in dendrogram *b* because they presented five common symptoms in the raw matrix, as well as *Empetrum nigrum* and *Vaccinium vitis-idaea*, which are linked because they both treat urinary problems.

In regard to both dendrograms obtained, the shape of dendrogram *b* followed the ranking of the species measured with SIV. *Pinus banksiana* is grouped with other families. Due to numerous zeros in the raw matrix it is thirteenth in the ranking test (see Table 3). It is less known and available in Whapmagoostui. Only Elders and Healers born in the southern part of Eeyou Istchee or inland were found to use the species (Blacksmith 1981; Zieba 1992; Leduc *et al.* 2006), because along the James and Hudson Bay, the Jack pine is absent (Farrar 1996).

The data sets from Whapmagoostui, Mistissini and Cree specific-literature have been compared using CA in order to perform the CT. The comparison of dendrograms illustrated in Figure 5 using the Jaccard coefficient showed similar groups of plant species, clustered together in the case of Whapmagoostui and in Cree-specific literature. Therefore, traditional knowledge is equivalent and medicinal plants used on these two cases treat the same T2D symptoms. For example, this is the case for *Rhododendron* spp. and Pinaceae. Also, due to the fact that weakness, back pain, infection sore/wounds (foot) are treated by *Pinus banksiana* in Whapmagoostui and inventoried from the literature, the OTUs are positioned at the same place in Figures 5a and b. In addition, there were no statistical significances between the other comparisons. Therefore, the dendrograms differ (Table 4). For example, since both spruces have the same degree of importance in Whapmagoostui which they treat same T2D symptoms, but not in Mistissini where *Picea glauca* is less used, they are clustered in Figure 5e but not in Figure 5f, respectively. This discrepancy and the one arising from *Picea glauca* influenced the grouping of species and therefore the statistic resulting from CT.

The clusters formed with dendrograms obtained in Figure 5 could potentially illustrate common secondary metabolites, especially plant-derived antioxidants listed by Larson (1988), Pratt (1992) and McCune and Johns (2002), as well as phenolic compounds (tannins and flavonoids), terpenoids and vitamins A, C and E. For instance, both dendrograms clustered *Picea* spp. This is probably due to the presence of ascorbic acid. Both species have terpenoids like other Pinaceae and Ericaceae (Arnason *et al.* 1981; Glasby 1991). The clustering of species from the same family based on the secondary compounds remains a hypothesis that needs to be confirmed by further phytochemical studies. CA demonstrates the capability to describe elementary phytochemistry in the context of ethnopharmacology. It is important to analyse these plants in order to understand their mode of action. Therefore, further analysis should be done in order to confirm the relationship between these fifteen species, particularly the Ericaceae and Pinaceae. These plants are also commonly used by other First Nations communities in other regions (Arnason *et al.* 1981).

5.4.2.3. Permutation tests

All three permutation tests performed in this study confirmed the results obtained with the Spearman's test, which compared the ranking of plants mentioned during the different surveys (Whapmagoostui and Mistissini) and in the Cree literature (see Table 4). Indeed, the homogeneity of the TM used in various Cree communities across Canada was seen both in the Mantel and Podani permutation tests and was also seen in CT (Whapmagoostui compared to the existing literature). Comparisons showed the strongest correlations with Podani test. Indeed, homogeneity between communities and between Mistissini and Literature was underlined. Using raw data instead of distance or similarity coefficients, the Podani algorithm probably reflects the true nature of these datasets. Also, the study shows that the use of different coefficients gives similar results, except for Euclidean distance.

The significant correlations obtained between plants used in Whapmagoostui and other western Cree communities (Wabasca, Siegfried [1994]; Muskekiwininiw-Asiniitniw, Zieba [1992]; wood Cree, Leighton [1985]) might be linked to the fact that all these communities are situated at the same latitude (East Cree Language 2005). They are part

of the northern boreal forest environment, where species repartition is susceptible of being similar among that of other Canadian provinces. For example, at the limit of the boreal forest, tamarack stands mostly in the northern areas, whereas balsam fir thrives mostly in the southern part (Farrar 1996). One can only assume that the choices of plants made by Cree are influenced by the abundance of the different species that lie within the environment adjacent to their community. The concordance in the results, however, suggests that there has been some conservation of the traditional knowledge despite the geographical and floristic gradients.

Therefore, the results here corroborate the findings of Leduc *et al.* (2006) and one can stipulate that, based upon the fifteen symptoms used in our survey, the same species are used for similar purposes among Cree communities throughout Canada.

5.5. Conclusions

The present study expanded and added new ethnobotanical information about Cree TM. A list of 26 medicinal plants, mainly from the Pinaceae and Ericaceae families, were mentioned by the Elders and Healers of Whapmagoostui during the interviews. This knowledge has been validated both scientifically and through interviews with informants who have verified its traditional medicinal use. Indeed, our list of prioritized species was corroborated by the antioxidant bioassays used (see Manuscript II) and by the comparison with the list obtained by Leduc *et al.* (2006), as well as the list extirpated from the literature on Cree TM.

Globally, Cree TM is quite homogenous with plants used for similar ailments throughout Canada, but locally, due to floristic and, quite possibly, cultural differences, some qualitative discrepancies can be seen, especially when the communities compared imply a North-South gradient, as is the case with Whapmagoostui and Mistissini.

Besides documenting Cree TM, this project has shown the importance of using quantitative and statistical tools for the interpretation and comparison of ethnobotanical data. Indeed, this study provides a solid framework for the further analysis of the most promising plants using phytochemical and pharmacological methods. Not only have

medicinal plants been ranked based on the calculation of a SIV, but this ranking correlates positively with the ranking obtained from the different bioassays. Post-validation with the Elders and Healers by returning to each community and addressing the importance of each plant through another set of interviews could add another interesting and valuable dimension to our project.

This preliminary evaluation of the Cree TM with the one done by Leduc *et al.* (2006) will allow the development of sound research in pharmacology and phytochemistry in order to further validate TM for T2D. Considering that oxidative stress is important in T2D (Salonen *et al.* 1995), antioxidants known to prevent the complications stemming from this disease (Baynes 1991) should be evaluated among the Cree medicinal plants. Phenolic compounds should also be investigated as well as antioxidant capacity. Such studies based on a multidisciplinary approach, and in which science and tradition meet can only benefit the health of the communities concerned. Introducing and implementing a complementary medicine more in harmony with the Cree traditional knowledge within the existing health clinics in Eeyou Istchee may reduce the rate of diabetes. In dealing with such an important and serious disease, one should seek an approach enriched with different knowledge systems, especially when dealing with T2D among First Nations who have already demonstrated traditional techniques that have proven successful at coping with certain symptoms.

6.0. Introduction to manuscript II

A list compiled of 26 medicinal plant species that treat T2D symptoms are used among Cree Eeyou Istchee of Mistissini and Whapmagoostui. Among these plant species, prioritized plants have been evaluated as the highest ranked in terms of TM for T2D treatment. Different secondary compounds contained in plants could arguably be the basis for the medicinal effects on T2D symptoms. Oxidative stress plays a role in diabetes complications (Salonen *et al.* 1995), but antioxidants, however, protect the oxidation damage on biological molecules (Maxwell 1995).

TM has been shown to have antioxidant properties (McCune 1999). The following manuscript is a report on the antioxidant potential of different plant extracts used among members of the Cree Nation and community in Québec. Three different bioassays to measure antioxidant activity, and one quantitative assay, were used to evaluate the phenolic content of these extracts. Results were compared together, and also with the previous ethnobotanical data on plant species from Mistissini and Whapmagoostui. This was done in order to validate the Cree Eeyou Istchee TM in terms of its antioxidant capacity and also to develop another priorized list of TM that includes plants with higher antioxidant activity for further analysis.

7.0. Manuscript II

Medicinal plants of Indigenous Cree communities (Québec, Canada): Antioxidant activity of plants used to treat Type 2 Diabetes symptoms.

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Abstract

The utilization of traditional plant-based medicine used by the Cree Nation of Eeyou Istchee for the treatment of Type 2 Diabetes (T2D) and related symptoms has been documented previously (Fraser *et al.* Manuscript I). As T2D is associated with systemic oxidative stress, habitual intake of plant tissue shown to be high in phenolic antioxidants assay aids in reducing health complications. The present study measures the antioxidant activity of traditional medicine (TM) by using the 1,1-diphenyl-2-pycryl-hydrozyl radical scavenging activity, conjugated dienes and thiobarbituric acid reactive substances bioassays. Water-soluble phenolic content was also measured. A total of twenty medicinal plants from Whapmagoostui and sixteen from Mistissini were compared to sixteen extracts of plants that were shown to have no medicinal value. Medicinal plant extracts, especially *Larix laricina* displayed high antioxidant activity, comparable to ascorbic acid, quercetin, epicatechin, catechin, Trolox® and also showed more antioxidant activity than many negative controls. Pinaceae and Ericaceae contain a significant level of phenolics. Also, years collected, the parts used and the source of extracts exhibited different antioxidant results. Positive correlations were found between the established traditional knowledge of Cree Elders and Healers and the antioxidant activity for medicinal plants used in Mistissini ($r = 0.3134$; $p = 0.058$) and in Whapmagoostui ($r = 0.5165$; $p = 0.001$). Significant correlations between phenolic content were also seen with the existing ethnobotanical data ($r = 0.5015$; $p = 0.003$) and bioassays ($r = 0.4178$; $p = 0.003$). The results support that a clear majority of plants used by the Cree are excellent sources of antioxidants. This report also screened antidiabetic plants for further *in vitro* and *in vivo* studies. Eventually, clinical trials could benefit from further analysis and testing of TM for reducing the severity of T2D complications arising from oxidative stress.

Keywords: Antioxidant activity; Cree; Diabetes; Medicinal plants.

7.1. Introduction

Type 2 Diabetes (T2D) is increasing worldwide and now affects approximately 171 million people (World Health Organization 2006). Canadian Indigenous people are at especially high risk (Young *et al.* 1985; Locke *et al.* 1993; Maberley *et al.* 2000), due to changes in traditional lifestyle and as a result of industrialization affe cting both the environment and also social and cultural norms (Berkes and Farkas 1978). The Cree Eeyou Istchee, are particularly affected by this disease (Robinson 1988; Robinson *et al.* 1995; Thouez *et al.* 1990), with a doubling of T2D rates over the past fifteen years, from 7 to 14 % (Brassard *et al.* 1993; CBHSS 2001).

T2D is a chronic disease related to insulin resistance and impaired glucose metabolism (World Health Organization 2006). Hyperglycemia (high glucose levels in blood plasma), T2D complications and oxidative stress have all been linked to diabetes. Indeed, the disease is characterized by chronic hyperglycemia and development of micro and macro vascular complications such as blurred vision and also artherosclerosis (Piconi *et al.* 2003). Among T2D complications, artherosclerosis is one of the major causes of death in T2D subjects, which has been mentioned by Scheffer *et al.* (2005). Other T2D symptoms have been listed by Leduc *et al.* (2006) and McCune and Johns (2002). Moreover, the complications of T2D have been attributed, among other factors, to the accumulation of advanced glycation end products (AGE) (Brownlee 1995) and oxidative stress (Baynes 1991). AGEs are also called sugar-derived modifications, since they involve the nonenzymatic modification of tissue proteins by physiologic sugars *in vivo* (Brownlee 1995). They are the initial products generated by glucose reaction known as glycation (Scheffer *et al.* 2005). Oxidative stress involves excess production of reactive oxygen species (ROS) (Opara 2002; Piconi *et al.* 2003). These mediators of cell injury are the initial products generated by oxidation. Therefore, the increase of glycoxidation and lipoxidation products, in the diabetic state, suggests a role for oxidative stress in T2D and its complications (Baynes and Thorpe 1999 and 2000; Giugliano *et al.* 1996).

Low-density-lipoprotein (LDL) aids in the transport of cholesterol in the blood to peripheral cells as has been described by Fruchart (1992). Duvall (2005) has explained

that LDL cholesterol and artherosclerosis are related; also, there is a relationship between LDL and T2D, which has been reviewed in work by Barakat *et al.* (1996). Modifications of native LDL in glycated LDL from AGEs and oxidised LDL from ROS, which are unstable and reactive molecules, are implicated in the development of the T2D (Scheffer *et al.* 2005). The mechanism of oxidative modification of the apolipoprotein, in presence of diabetes, has been shown. Glycoxidation and lipoxidation products lead to the retention of LDL in the vascular walls, enhance uptake of oxy-LDL by macrophage, and this accumulation results in the formation of foam cells and eventually further tissue damage such as endothelial dysfunction (Baynes and Thorpe 2000; Scheffer *et al.* 2005). Lipid peroxidation, occurring within the vascular walls, releases residual advanced lipoxidation end-products, a precursor implicated in the development of artherosclerosis. This process, which implicates oxy-LDL, could therefore provide a possible explanation for the increased risk of artherosclerosis among T2D patients (Baynes and Thorpe 2000; Levy *et al.* 2000).

Antioxidants have been implicated as therapeutic aids for numerous diseases, such as, artherosclerosis, cancer and cardiovascular complications associated with late-stage T2D. This is due to their ability to inhibit the negative effects of ROS (Salonen *et al.* 1995; Halliwell 1997; Cunningham 1998; Baynes and Thorpe 1999; Cai *et al.* 2004). A rich supply of antioxidants, such as, flavonoids and related phenolic compounds, vitamins C and E, are contained in fruits, vegetables, spices and medicinal plants (Chipault *et al.* 1952; Arnason *et al.* 1981; Larson 1988; Pratt 1992; Proteggente *et al.* 2003; Katsube *et al.* 2004). The consumption of antioxidants has been shown to improve certain pathologies of T2D patients (Farvid *et al.* 2005) and even control metabolic oxidative status (Douillet *et al.* 1998). Likewise, supplementation with antioxidants from both vitamin C and vitamin E on human subjects has also shown to be effective in inhibiting the *in vitro* oxidation of LDL (Rifici and Khachadurian 1993). More specifically, ascorbic acid (vitamin C) and α-tocopherol (vitamin E) have shown an ability to inhibit *in vitro* Cu-mediated lipid peroxidation of LDL by ROS trapping of malondialdehyde (MDA) and conjugated diene (CD) products (Babiy *et al.* 1990; Jialal *et al.* 1990; Halliwell 1997; Esterbauer *et al.* 1989; Esterbauer *et al.* 1991). The above mentioned evidence supports

the plausibility for treatment of T2D and its complications with antioxidant therapies (Opara 2002).

Traditional medicine (TM), such as medicinal plants, continues to be used worldwide by many aboriginal and First Nations people (West 1974; Marshall *et al.* 1989). Furthermore, 1200 antidiabetic plant species, used around the world among diverse Native groups have been reviewed for the treatment of T2D symptoms, where over 80 % of 295 species have shown strong evidence of hypoglycemic activity (Marles and Farnsworth 1995). The work of McCune and Johns (2002) has shown particular interest in the use of TM by First Nations people in Canada. They have assessed 35 medicinal plants and compared them with commercial products, showing that there was effective antioxidant potential of boreal TM associated with T2D symptoms. Since T2D affects the health of many Native groups in Québec such as the Cree Nation (CBHSS 2001), recent ethnobotanical and collaborative studies have looked at TM use among the Cree of Mistissini (Leduc *et al.* 2006) and Whapmagoostui (Fraser *et al.* Manuscript I) respectively. Research from both studies has shown that TM is currently used in both regions for treatment of T2D symptoms.

The study evaluated the antioxidant activity of Cree medicinal plants like those found in the studies of Leduc *et al.* (2006) and Fraser *et al.* (Manuscript I). A comparative analysis was undertaken with non-medicinal plants, and also between different categories of plants in order to assess a correlation with antioxidant capacity, water-soluble phenolic content and in order to provide insight into the findings from previous ethnobotanical information. Human *in vitro* LDL model was used on plant extracts and was submitted to lipid peroxidation and then compared to well known antioxidants, such as vitamins C and E.

This study is the introduction to a long-term project with the goal of screening additional antidiabetic plants for further research similar to the previous study done by Spoor *et al.* (2006) that assessed *in vitro* the antidiabetic potential of the eight Cree TM with the most promising antioxidant results. Indeed, other *in vitro* studies than that of Grandi (2006)

will be undertaken in the future, as well further *in vivo* experiments with animals and eventually clinical studies will be realized. This collaborative research is being done with the aim of promoting the use of TMs among the Cree and also as a possible complementary strategy in the treatment and control of T2D complications.

7.2. Material and Methods

7.2.1. Plant extracts

Ethnobotanical studies were carried out in two Cree communities in Northern Québec in the summers of 2003-2004 (Leduc *et al.* 2006; Fraser *et al.* Manuscript I). Elders and Healers were interviewed concerning medicinal plants, which were known to treat fifteen symptoms of T2D. Most of the time, they used specific plant tissues, for example berries, needles, inner bark, etc. Fresh material was gathered in different plant populations or individuals, for a total of 5, in order to obtain genetical/phytochemical variability within the extracts. Plant species with no medicinal value were chosen for randomized selection from Whapmagoostui as a negative control to compare antioxidant activity with medicinal plants. Voucher specimens were deposited at the Herbier Marie-Victorin of Montréal, the Cree Cutural Institute at Oujé-Bougoumou and in schools of both Mistissini and Whapmagoostui. Fresh plant material, stored at - 4 °C, was used for lyophilisation. The lyophilized material was finely ground (2 mm) before ethanolic extraction (10 g: 210 ml) using the Soxtec extraction system®HT2. The ethanol was removed by rotaevaporation using a Büchi® 461 Switzerland, freeze-dried and stored at - 20 °C in amber vials with teflon-lined caps. Then, only a small amount of each extracts was used for analyses.

7.2.2. Reagents

Trolox®, a water-soluble analog of vitamin E, ascorbic acid, catechin, quercetin, epicatechin, thiobarbituric acid (TBA), trichloroacetic acid (TCA), ethylenediaminetetraacetic acid (EDTA), butylated hydroxytoluene (BHT), 1,1,3,3-tetraethoxypropane or malondialdehyde (MDA), sodium hydroxide (NaOH), copper ($CuSO_4$), Folin-Ciocalteau reagent and sodium carbonate (Na_2CO_3) were obtained from Sigma-Aldrich, Canada. Sodium phosphate diabasic anhydrous (Na_2HPO_4) and sodium phosphate monobasic monohydrate ($Na_2HPO_4.H_20$) were purchased from Acros, USA.

1,1-diphenyl-2-pycryl-hydrozyl (DPPH) was obtained from TCI America Portland, USA. LDL concentration was determined with a Sigma Diagnostics protein assay kit including bovine standard albumin (BSA), Lowry solution and Folin & Ciacalteu's phenol reagent (Sigma) using Sephadex PD-10 (Sigma). Human LDL was purchased from Biolynx (Canada) and Intracell (USA).

7.2.3. 1,1-diphenyl-2-pycryl-hydrozyl free radical scavenging activity

1,1-diphenyl-2-pycryl-hydrozyl (DPPH) free radical scavenging activity was measured according to the procedure described by Blois (1958) and Cotelle *et al.* (1996), with subsequent modifications by McCune and Johns (2002) and Owen and Johns (2002). Different concentrations of extract were dissolved in 0.5 ml EtOH to which 3 ml of 100µM DPPH was added. The reaction was allowed to stand for ten minutes at room temperature. Absorbance at 517 nm ($A_{517\ nm}$) was measured using a Beckman DU® 640 spectrophotometer (USA). An IC_{50} was calculated from the linear portion of the dose-response curve obtained from ascorbic acid. This value is the concentration required to inhibit the absorbance by 50 %. An approximate value to determine the scavenging activity is based on the work of Acuna *et al.* (2002), Lee *et al.* (2003) and Yokozawa *et al.* (1998). Below 25 ppm, plants are considered *very strong* scavengers; 25-50 ppm as *strong*; 50-100 ppm as *moderate* and finally *no activity* for > 100ppm. Cathecin, epicatechin and quercetin were used as the positive controls.

7.2.4. Low-density lipoprotein determination

Human LDL dissolved in 1mM PBS (0.175g Na_2HPO_4 and 1.05g $Na_2HPO_4.H_20$ in 1000g millipore water, pH 7.4) was passed through a Sephadex PD-10 (Sigma) to remove EDTA and NaCl. The final concentration obtained was 100 µg / ml.

7.2.5. Conjugated dienes formation

Conjugated dienes analysis was carried out according to Esterbauer *et al.* (1989) with subsequent modifications. 96-well UV-transponent microtiter plates were filled with 5 ppm plant extracts, 15 µM $CuSO_4$ and EDTA / NaCl-free human LDL dissolved in 1mM PBS. Absorbance at 234 nm ($A_{234\ nm}$) was monitored every 5 min for 15 hours to verify the increase using a µQuant™ Instruments (USA). A lag time was calculated as the

intersection with the propagation phase, described by Esterbauer *et al.* (1989 and 1990). Ascorbic acid (28.39μM) and Trolox® (19.98μM) were used as positive controls.

7.2.6. Thiobarbituric acid reactive substances assay

Thiobarbituric acid reactive substances (TBARS) were measured following the method of Sobal *et al.* (2000). 5 ppm of plants extracts and EDTA / NaCl-free LDL dissolved in 1mM PBS were incubated for one hour at room temperature. The oxidation of LDL was initated with $CuSO_4$. After the addition of the oxidant, 120 μl of solution mixture (total volume 500 μL) was removed immediately, and again after 90 min, 180 min and 240 min. At each end point, 10 μl 400 μM EDTA dissolved in 1 M NaOH and 10 μl 10 μM BHT were added and the solution was put on ice. Thereafter, 50 μL 50 % (w / v) TCA and 75 μL of 1.3 % (w / v) TBA dissolved in 0.05M NaOH were added. The solution was incubated at 60°C for 40 min, put on ice and centrifuged at 2000g for 5 min. Then, 200 μl of supernatant was removed and transferred to a 96-well microtiter plate. Fluorescence was measured at excitation wavelength (510 nm / emission wavelength 553 nm), using a Flex Station ™ II Molecular Devices (USA). The amount of TBARS released in nmol MDA equivalents / mg LDL protein along the end points was determined from a standard curve of 1,1,3,3-tetraethoxypropane. Ascorbic acid (28.39μM) and Trolox® (19.98μM) were used as positive controls.

7.2.7. Water-soluble phenolics

The amount of total water-soluble phenolics was determined with the Folin-Ciocalteu colorimetric assay (Singleton and Rossi 1965) with the following modifications: samples were diluted with water at a 1:10 ratio. Five ml of Folin-Ciocalteau reagent, 1: 10 with distilled water, were added to 1 ml aliquot of the diluted sample, mixing well and placed for 3-8 mins at room temperature. Subsequently, 4 ml of 7.5 % sodium carbonate solution was added. After two hours at room temperature and in darkness, color development at Absorbance at 725 nm ($A_{725\ nm}$) was determined using a Beckman DU® 640 spectrophotometer (USA). The intensities of sample color are shown as polyphenol concentration expressed in μg of phenolic / mg of extracts, based on the standard curve of quercetin calculated from the linear portion of the dose-response curve.

7.2.8. Statistical analysis

Results represent mean ± SEM of at least n = 3 independent experiments performed in duplicate. Data from DPPH, CD bioassays and phenolic content experiment were performed with one-way analysis of variance (ANOVA), and those from TBARS bioassay were performed with one-way repeated measure. The differences between means were tested using a post-hoc LSD multiple comparison. The significance of Fisher analysis was set at $P < 0.05$.

7.2.8.1. Comparisons

For each assay, results were compared with different groups of plants. Groups with more than twenty samples, such as medicinal and non-medicinal plant species of Whapmagoostui, and medicinal plant species of both communities, were compared with the Student t-test. To compare groups with less than twenty samples, such as within the same family (non-medicinal and medicinal plants), the same plant species (different plant parts, communities and years) different statistical tests were performed. Mann Whitney (independent) or Wilcoxon (related) compared the two groups together. Kruskal Wallis (independent) or Tukey tests (related) compared more than two groups.

7.2.8.2. Ranking

Each plant species was ranked according to their antioxidant activity in the bioassays. Linear regression analysis expressed with Spearman's correlation coefficient (r) was performed between bioassays. Another ranking method was also used in order to compare results from bioassays with the Syndromic Importance Value (SIV) obtained in the ethnobotanical survey (Fraser *et al.* Manuscript I) and with phenolic content. The centered reduced value is a unique rank given for each plant species sample, which is the mean of normalized measures that are obtained among the three antioxidant bioassays (DPPH, CD and TBARS). Then, the importance in antioxidant activity of each sample becomes comparable with the SIV. On its own, SIV is a rank value associated with each medicinal plant, calculated with the frequency of mention by participants, the weight of each fifteen symptoms studied, and the number of persons interviewed (Fraser *et al.* Manuscript I). The compositional analysis ranking was calculated independently in order

to be compared with individual bioassay ranking and the SIV. SAS 9.0 were used for the analysis.

7.3. Results

7.3.1. Bioassays

Table 1 lists each sample studied, whether related (medicinal plant species) or not (non-medicinal plant species) to the treatment of T2D symptoms. This list includes their scientific name, abbreviation, plant families, parts used, where and when the material was collected, extract yield, herbarium number and the unique rank from bioassays results. From twenty plant families, a total of twenty medicinal plants from Whapmagoostui, sixteen from Mistissini and sixteen extracts of plants with no medicinal value were studied in relation to antioxidant activity.

DPPH results (Table 2) demonstrated that among 52 plant samples, 51.92 % of extracts have statistically similar scavenging activity to known antioxidants such as ascorbic acid (3.84 ± 0.01 ppm), quercetin (4.42 ± 0.23 ppm), catechin (5.56 ± 0.37 ppm) and epicatechin (5.94 ± 0.18 ppm). Specifically, 62.5 % and 55 % of medicinal plants of Mistissini and Whapmagoostui and 37.5 % of non-medicinal plants showed activity. Plants extracts that displayed strongest activity in the DPPH assay were *Pinus banksiana*-cone (7.44 ± 0.29 ppm), *Salix planifolia*-bark (11.47 ± 0.37 ppm) and *Chamerion angustifolium* (9.11 ± 0.35 ppm). 59.6 % of plant species tested presented an IC_{50} below 25 ppm, therefore making them effective radical ion scavengers. The majority of medicinal plants in both communities (except *Lycopodium clavatum, Cladonia rangiferina, Leymus mollis, Vaccinium vitis-idaea, Populus balsamifera* and gum of spruce), presented better scavenging activity than non-medicinal plants ($p = 0.001$). Indeed, the IC_{50} of many negative controls was greater than 50 ppm.

As listed in Table 2, a total of 49 plant samples were studied in the CD assay. Gums of *Picea glauca* and *Picea mariana* interfered with the assay and these samples could not be measured effectivly. Therefore, these were excluded from the analysis. 29.78 % and 44.68 % of studied plants in CD assay presented longer lag time than Trolox® and

ascorbic acid, respectively, indicating greater antioxidant activity than these references analog to vitamins E and C, respectively. More than half of the samples had a lag time statistically similar to both Trolox® and ascorbic acid (see statistic in Table 2). *Larix laricina* (187.65 ± 12.63 min Mist. and 182.42 ± 5.34 min Whap.) and *Loiseleuria procumbens* (164.57 ± 5.32 min Non-Medi) displayed the highest antioxidant activity in this assay.

The majority of the 49 plant samples analysed in the TBARS assay showed antioxidant activity as represented by a low production of TBARS (Table 2). In comparison with Trolox®, more than 59.18 % had better antioxidant activity and 73.47 % were statistically similar. The strongest antioxidant activity was observed in *Pinus banksiana*-cone (Mistissini), *Chamerion angustifolium* (Non-Medicinal) and *Juniperis communis*-root (Whapmagoostui).

7.3.2. Water-soluble phenolics

Figure 1 illustrates total water-soluble phenolic content among medicinal plant extracts. Among twenty-four medicinal plants studied, *Kalmia angustifolia* (599.0 ± 8.1 µg of phenolic / mg of extracts) contained the highest phenolic levels and *Vaccinium vitis-idaea* (47.7 ± 1.5 µg of phenolic / mg of extracts) had the lowest.

7.3.3. Comparisons

The groups of plants have shown differences statistically according to their antioxidant capacity. First, medicinal plants from Whapmagoostui had higher antioxidant potential than non-medicinal plants in the TBARS assay ($p = 0.0001$), but not in DPPH and CD. Secondly, TM used in Whapmagoostui had higher antioxidant potential in comparison with medicinal plants used in Mistissini based on the TBARS ($p = 0.0001$) and CD ($p = 0.034$) results.

Figure 2 illustrates examples of DPPH results, Figure 3 shows examples of CD results and Figure 4 points up examples of TBARS results comparing different groups of sample extracts. These include families, medicinal (M) species versus non-medicinal (NM), different parts used from *Juniperus communis,* the same species from both studied

communites (Whapmagoostui and Mistissini); and, (Figures 2 and 4 only) the different years of collection for *Sorbus decora.* Statistical tests applied were: Mann Whitney (1), Kruskal-Wallis (2) and Tukey (3) for Salicaceae (1) (Figs. 2a and 3a), Ericaceae (2) (Figs. 2a and 3a), *Juniperus communis* (3) (Figs. 2b and 3c), both studied communites (1) (Figs. 2c and 3b) and *Sorbus decora* (1) (Fig. 2d).

Antioxidant activity among medicinal plants of Salicaceae and Ericaceae were higher than non-medicinal plants (Figs. 2a and 3a), where results from Sphagnaceae and Lichenophyta species were statistically similar. Salicaceae and Ericaceae had similar TBARS production (Fig. 4a) below 15 nmol MDA eq. / mg protein.

Juniperus communis-roots, *Picea glauca*-needles-cones and *Sorbus decora*-stems had better activity than berries-stems, gum, and leaves, respectively. Figures 2b, 3c and 4b illustrate *Juniperus communis*-roots with higher scavenging activity, longer lag time and lower TBARS production than needles.

The extracts of *Pinus banksiana* and of *Rhododendron groenlandicum* from Mistissini showed higher DPPH scavenging activity than extracts from Whapmagoostui, whereas extracts of *Larix laricina* from Whapmagoostui had higher activity than the extract from Mistissini (Fig. 2c). However, the opposite observation could be found from the CD assay. Indeed, Jack pine and tamarack from Whapmagoostui and Mistissini, respectively, showed higher antioxidant activity, whereas lag times of both Labrador teas (*Rhododendron* spp.) are statistically similar (Fig. 3b). In the case of TBARS formation, they are all similar, with the exception of *Larix laricina* (Mist.) that projected an increase of TBARS (Fig. 4c).

Extract of *Sorbus decora,* collected in 2004 in Mistissini, presented higher antioxidant activity than the extract collected in 2003 (Figs. 2d and 4d).

Figure 5 presents the lipid peroxidation by the level of TBARS production among the reference materials. Ascorbic acid produced an abundant quantity of TBARS comparable

to the control (LDL-$CuSO_4$). The oxidation products on LDL were delayed by medicinal plant extracts (Fig. 4a) and Trolox® (Fig. 5), illustrated by a plateau in the time, whereas the oxidation products on LDL increased expodentially in terms of time in the presence of non-medicinal plants such as *Loiseleuria procumbens* (Fig. 4a), ascorbic acid and the control (Fig. 5).

Statistically significant differences in phenolic content were seen between Pinaceae species, Ericaceae species and Picea organs, with *Pinus banksiana, Kalmia angustifolia* and *Picea glauca*-cone, which contained high phenolic levels (Fig. 1).

7.3.4. Ranking

The Spearman's coefficient of rank correlation test between the ranking of each plants among TBARS and DPPH had a value of 0.7811 ($p = 0.000$). In addition, the other ranking test, based on the unique rank of each plant species from the three bioassays, is illustrated in Table 1. *L. laricina* (Whap. and Mist.) and *Loiseleuria procumbens* (Non-Medicinal) had high positions: 1, 3 and 4 respectively, corresponding to an elevated antioxidant activity. Medicinal plants from both communities had stronger antioxidant potential than non-medicinal plants, where 38.78 % of medicinal extracts were among the twenty-five highest ranked in comparison of 12.24 % of non-medicinal samples. Also, fourteen of the most effective twenty-five extracts in terms of antioxidant activity can be found within the Ericaceae and Pinaceae plant families. Figure 6 shows positive correlations in Whapmagoostui $r = 0.5165$ ($p = 0.001$) and in Mistissini $r = 0.3134$ ($p = 0.058$) in relation to the ranking from the bioassay and the ranking from the ethnobotanical survey, the SIV (Fraser *et al.* Manuscript I). Finally, Figure 7 describes the positive correlations of phenolic content with the ranking obtained among bioassays ($r = 0.4178$; $p = 0.003$) and the ethnobotanical survey ($r = 0.5015$; $p = 0.003$). Only TBARS and DPPH showed positive correlations with phenolic content.

Table 1. Plants used (medicinal) and not used (non-medicinal) in relation to the treatment of T2D symptoms : scientific names, families, parts used, where and when the material was collected, extract yields, herbarium numbers and ranking according to the bioassays results.

Scientific name	(Abbreviation)	Families	Plant parts [a]	Communities (Label) [b]	Year collected	Extract Yields (%) w / w	Herbarium No.	Ranking No. [c]
MEDICINAL PLANTS								
Abies balsamea (L.) Mill.	(Ab)	Pinaceae	Ca	M	2003	---	2003-01	27
Alnus incana subsp. *rugosa* (Du Roi) R.T. Clausen	(Ar)	Betulaceae	Ca	M	2003	---	2003-04	33
Cladonia rangiferina (L.) Wigg.	(Cr)	Lichen	A	W	2004	5.69	2004-51	49
Empetrum nigrum L.	(En)	Empetraceae	Be	W	2004	45.66	2004-05	48
Gaultheria hispidula (L.) Muhl. [d]	(Gh)	Ericaceae	Be	M	2003	---	2003-07	36
Juniperus communis L.	(Jc)	Cupressaceae	Be	W (1)	2004	46.66	2004-06	28
Juniperus communis L.	(Jc)	Cupressaceae	N	W (2)	2004	28.07	2004-06	29
Juniperus communis L.	(Jc)	Cupressaceae	R	W (3)	2004	5.07	2004-06	2
Kalmia angustifolia L.	(Ka)	Ericaceae	L	M	2004	32.8	2003-13	25
Larix laricina (Ru Roi) K. Koch.	(Ll)	Pinaceae	Ba	M (1)	2003	---	2003-12	---
Larix laricina (Ru Roi) K. Koch.	(Ll)	Pinaceae	Ba	M (2)	2004	4.856	2004---	3
Larix laricina (Ru Roi) K. Koch.	(Ll)	Pinaceae	Ca	W (3)	2004	37.89	2004-11	1
Leymus mollis Trin.	(Lm)	Poaceae	A	W	2004	10.18	2004-08	39
Lycopodium clavatum L.	(Lc)	Lycopodiaceae	A	M	2004	15.29	2003-31	40
Picea glauca (Moench) Voss	(Pg)	Pinaceae	Co	W (1)	2004	49.85	2004-12	8
Picea glauca (Moench) Voss	(Pg)	Pinaceae	G	W (2)	2004	86.96	2004-12	20
Picea glauca (Moench) Voss	(Pg)	Pinaceae	N	W (3)	2004	24.5	2004-12	7
Picea mariana (Mill.) B.S.P.	(Pm)	Pinaceae	Co	M (1)	2003	---	2003-15	31
Picea mariana (Mill.) B.S.P.	(Pm)	Pinaceae	G	W (2)	2004	91.25	2004---	22

Table 1. *Continued*

Scientific name	(Abbreviation)	Families	Plant parts [a]	Communities (Label) [b]	Year collected	Extract Yields (%) w / w	Herbarium No.	Ranking No. [c]
MEDICINAL PLANTS								
Pinus banksiana Lamb.	(Pb)	Pinaceae	Co	M (1)	2003	---	2003-14	23
Pinus banksiana Lamb.	(Pb)	Pinaceae	Co	W (2)	2004	6.77	2004-03	18
Populus balsamifera L.	(Psp.)	Betulaceae	Ca	M	2004	13.87	2003-49	32
Rhododendron groenlandicum (Oeder) Kron et Judd	(Rg)	Ericaceae	L	M (1)	2003	---	2003-02	---
Rhododendron groenlandicum (Oeder) Kron et Judd	(Rg)	Ericaceae	L	M (2)	2004	16.8	2004---	19
Rhododendron groenlandicum (Oeder) Kron et Judd	(Rg)	Ericaceae	L	W (3)	2004	24.2	2004-15	17
Rhododendron tomentosum (Stokes) Harmaja ssp. *subarcticum* (Harmaja) G. Wallace	(Rt) (Rt)	Ericaceae	L	W	2004	17.35	2004-33	15
Salix planifolia Pursh ssp. *Planifolia*	(Spp)	Salicaceae	Ba	W	2004	25.95	2004-37	16
Sarracenia purpurea L.	(Sp)	Sarraceniaceae	L,R	M (1)	2004	4.515	2004---	24
Sarracenia purpurea L.	(Sp)	Sarraceniaceae	L,R	M (2)	2003	---	2003-05	---
Sorbus decora C.K.Schneid.	(Sd)	Rosaceae	Ba	M (1)	2004	4.453	2004-14	12
Sorbus decora C.K.Schneid.	(Sd)	Rosaceae	Ba	M (2)	2003	---	2003-10	5
Sorbus decora C.K.Schneid.	(Sd)	Rosaceae	L	W (3)	2004	25.65	2004-14	46
Sorbus decora C.K.Schneid.	(Sd)	Rosaceae	S	W (4)	2004	12.36	2004-14	9
Sphagnum fuscum (Schimp.) Klinggr.	(Sf)	Sphagnaceae	A	W	2004	0.85	2004-77	37
Vaccinium vitis-idaea L. var *minus* Lodd.	(Vvv)	Ericaceae	Be	W	2004	48.4	2004-21	34
Vaccinium uliginosum L. var. *alpinum* Bigel.	(Vu)	Ericaceae	R	W	2004	10.48	2004-20	6

Table 1. *Continued*

Scientific name	(Abbreviation)	Families	Plant parts [a]	Year collected	Extract Yields (%) w / w	Herbarium No.	Ranking No. [c]
NON-MEDICINAL PLANTS [e]							
Achillea borealis Bong.	(*Ab*)	Asteraceae	A	2004	1.79	2004-29	38
Armeria maritima (P. Mill.) Willd. ssp. *sibirica* (Turcz. ex Boiss.) O. Hyl.	(*Am*)	Plombaginaceae	A	2004	3.80	2004-09	41
Betula grandulosa Michx.	(*Bg*)	Betulaceae	L	2004	29.35	2004-02	21
Campanula rodundifolia L.	(*Cr*)	Campanulaceae	A	2004	26.35	2004-07	30
Chamerion angustifolium (L.)Holub	(*Ca*)	Onagraceae	A	2004	15.84	2004-17	13
Equisetum arvense L.	(*Ea*)	Equisetaceae	A	2004	8.44	2004-32	45
Hippuris vulgaris L.	(*Hv*)	Haloragaceae	A	2004	15.54	2004-23	10
Honckenya peploides (L.) Ehrh.	(*Hp*)	Crassulaceae	A	2004	8.04	2004-59	47
Loiseleuria procumbens (L.) Desv.	(*Lp*)	Ericaceae	A	2004	27.05	2004-75	4
Myrica gale L.	(*Mg*)	Myricaceae	L, S	2004	4.8	2004-36	14
Rhytidium rugosum (Hedw.) Kindb.	(*Rr*)	Sphagnaceae	A	2004	2.045	2004-38	42
Rubus chamaemorus L.	(*Rc*)	Grossulariaceae	A	2004	33.1	2004-58	26
Salix arctophila Cock. ex Heller	(*Sa*)	Salicaceae	S, Ba	2004	25.65	2004-55	35
Sphagnum russowii Warnst.	(*Sr*)	Sphagnaceae	A	2004	1.59	2004-34	11
Stereocaulon paschale (L.) Hoffm.	(*Sp*)	Lichenophyta	A	2004	7.88	2004-76	44
Tanacetum bipinnatum (L.) Schultz-Bip. ssp. *huronense* (Nutt.) Breitung	(*Th*)	Asteraceae	A	2004	11.89	2004-19	43

[a] Abbreviations of part used : all (A); bark (BA); berries (BE); cambium (CA); cone (CO); gum (G); leaf (L); needle (N); stem (S); root (R);
[b] Mistissini (M), Whapmagoostui (W)
[c] The ranking method measured the individual rank of plants species which is the mean of normalized value of each plants obtained among bioassay, where 1 is the strongest plant in antioxidant activity and the 47 is the lowest.
[d] Only leaves were collected as fresh material.
[e] Non-medicinal plants were provided in Whapmagoostui.

Table 2. Antioxidant activity of traditional plants used by CEI in Mistissini and Whapmagoostui according to three different bioassays (diphenyl-2-pycryl-hydrozyl (DPPH) radical, conjugated dienes (CD) and thiobarbituric acid reactive substances (TBARS). Results are expressed by mean ± SEM of duplicate samples assayed at least in triplicate. Specifically, units are IC50 (ppm) for DPPH, lag time (min) for CD and nmol MDA equivalent / mg LDL protein for TBARS.

Scientific name (Label) [1]	DPPH [2]	CD [2]	TBARS [2,3]			
			0 min	90 min	180 min	240 min
LDL		No lag time	3.010 ± 1.23 [a]	4.43 ± 1.91	2.65 ± 1.42	1.567 ± 1.01
Control		102.61± 2.28 [j,kl]	2.61 ± 1.01 [r,s,t]	47.82 ± 9.15	158.29 ± 16.52	201.92 ± 12.39
Trolox		130.59 ± 9.84 [f,g,h]	0.75 ± 0.27 [a,b,c,d,e]	12.20 ± 1.05	37.52 ± 4.95	48.33 ± 4.05
Ascorbic acid	3.84 ± 0.01 [a]	108.26 ± 3.13 [i,j]	4.04 ± 3.48 [s,u]	42.89 ± 3.48	166.17 ± 19.84	204.32 ± 10.91
Quercetin	4.42 ± 0.23 [a,b]	---	---			
	10.80 ± 1.75 uM					
Catechin	5.56 ± 0.37 [a,b,c]	---	---			
	15.10 ± 2.47 uM					
Epicatechin	5.94 ± 0.18 [a,b,c]	---	---			
MEDICINAL PLANTS						
A. balsamea	28.72 ± 1.63 [a,b,c,d,e]	117.45 ± 10.27 [f,g,h,i]	6.34 ± 2.58 [g,k,l,m,n,o]	0.41 ± 0.80	0.82 ± 1.043	33.83 ± 3.84
A. incana ssp. *rugosa*	9.30 ± 0.48 [a,b,c]	53.09 ± 8.26 [t,u,v,w]	2.14 ± 1.49 [a]	2.71 ± 1.87	6.34 ± 2.58	0.41 ± 0.46
C. rangiferina	636.47 ± 23.54 [n]	146.83 ± 10.72 [c,d,e,f]	5.54 ± 0.18 [o,q,r,t]	43.33 ± 3.13	120.97 ± 13.80	167.79 ± 10.94
E. nigrum	86.32 ± 1.80 [f,g]	108.42 ± 2.12 [i,j,k]	5.08 ± 0.86 [u]	58.46 ± 3.65	215.6 ± 16.34	266.3 ± 15.04
G. hispidula	25.44 ± 1.24 [a,b,c,d,e]	52.08 ± 6.03 [u,v,w]	2.15 ± 0.29 [a]	11.29 ± 2.22	11.55 ± 2.61	7.16 ± 2.14
J. communis (1)	30.31 ± 1.45 [a,b,c,d,e]	84.64 ± 1.85 [m,n,o,p,q,r]	6.02±2.64 [a,b,c,d,e]	9.39 ± 2.52	27.39 ± 11.08	39.48 ± 14.97
J. communis (2)	30.56 ± 0.61 [b,c,d,e]	71.51 ± 9.02 [q,r,s,t,u]	4.99±1.05 [a]	9.28 ± 1.27	6.50 ± 0.98	6.13 ± 0.23
J. communis (3)	15.15 ± 0.36 [a,b,c,d]	167.76 ± 12.97 [a,b,c]	3.11±2.30 [a]	7.41 ± 2.98	5.91 ± 1.86	5.19 ± 0.91
K. angustifolia	14.22 ± 0.60 [a,b,c]	70.78 ± 8.15 [q,r,s,t,u,v]	3.76±1.87 [a]	4.85 ± 1.54	5.24 ± 0.93	5.15 ± 2.34
L. laricina (1)	31.52 ± 0.37 [b,c,d,e]	---				
L. laricina (2)	41.54 ± 0.96 [c,d,e]	187.65 ± 2.63 [a]	6.38±2.14 [a,b,c,d,e]	22.44 ± 2.52	62.84 ± 17.80	48.33 ± 2.68

Table 2. *Continued*

Scientific name (Label) [1]	DPPH [2]	CD [2]	TBARS [2,3]			
			0 min	90 min	180 min	240 min
MEDICINAL PLANTS						
L. laricina (3)	29.95 ± 1.27 [b,c,d,e]	182.42 ± 5.34 [a,b]	4.97±1.73 [a]	8.92 ± 2.02	11.80 ± 2.90	6.91 ± 1.15
L. mollis	316.28 ± 20.99 [k]	158.89 ± 2.87 [c,d,e]	4.73±0.87 [n,q,r,t]	52.08 ± 4.31	136.28 ± 18.40	161.26 ± 22.71
L. clavatum	698.78 ± 74.28 [o]	180.96 ± 10.69 [a,b]	4.76±1.45 [d,f,g,h,i,j]	35.15 ± 2.41	62.76 ± 4.64	79.85 ± 3.08
P. glauca (1)	18.93 ± 0.69 [a,b,c,d,e]	115.26±2.83 [h,i,j]	5.35±3.56 [a]	8.45 ± 1.25	7.19 ± 0.92	5.39 ± 0.74
P. glauca (2)	124.35 ± 6.53 [i]	No lag time	5.83±0.86 [a,b,c]	21.24 ± 1.61	30.97 ± 11.29	29.56 ± 1.54
P. glauca (3)	23.67 ± 1.06 [a,b,c,d,e]	133.36 ± 2.87 [f,g,h]	1.64±1.66 [a,b]	20.81± 4.20	11.10 ± 2.67	6.19 ± 1.64
P. mariana (1)	8.68 ± 0.19 [a,b,c]	60.66 ± 7.83 [s,t,u,v,w]	2.15±0.24 [a]	6.86 ± 2.45	4.49 ± 0.10	3.45 ± 0.81
P. mariana (2)	136.55 ± 3.94 [i]	No lag time	6.64±1.87 [a,b,c]	19.33 ± 2.93	29.33 ± 7.64	24.11 ± 4.04
P. banksiana (1)	7.44 ± 0.29 [a,b,c]	74.22 ± 0.79 [q,r,s,t]	0.68±0.96 [a]	4.62 ± 1.96	2.39 ± 0.80	-0.57 ± 0.13
P. banksiana (2)	14.98 ± 0.46 [a,b,c,d]	84.48 ± 2.98 [n,o,p,q,r]	3.51±1.15 [a]	9.39 ± 2.15	5.84 ± 0.31	3.76 ± 0.34
P. balsamifera	120.24 ±5.00 [i]	102.65 ± 2.91 [j,k,l,m,n]	4.42±2.07 [b,f,g,h,I,j]	23.46 ± 7.83	50.10 ± 38.80	65.66 ± 55.06
R. groenlandicum (1)	14.85 ± 0.93 [a,b,c,d]	80.95 ± 9.37 [o,p,q,r,s]	6.54±1.53 [a]	7.57±2.78	5.53 ± 1.52	4.52 ± 1.70
R. groenlandicum (2)	15.77 ± 1.37 [a,b,c,d]	---	---			
R. groenlandicum (3)	19.55 ± 0.69 [a,b,c,d,e]	87.74 ± 10.77 [k,l,m,n,o,p,q]	4.69 ± 1.02 [a]	12.86 ± 4.43	6.38 ± 0.00	6.85 ± 1.02
R. tomentosum ssp.*subarcticum*	20.63 ± 0.65 [a,b,c,d,e]	89.74 ± 2.14 [k,l,m,n,o,p,q]	4.76 ± 1.63 [a]	7.31 ± 0.00	8.70 ± 1.00	5.28 ± 1.85
S. planifolia ssp.*planifolia*	11.47 ± 0.37 [a,b,c]	86.45 ± 2.45 [l,m,n,o,p,q]	7.61 ± 3.88 [a]	9.61 ± 1.79	12.83 ± 2.92	3.85 ± 0.00
S. purpurea (1)	27.65 ± 0.77 [a,b,c,d,e]	77.22 ± 7.88 [p,q,r,s]	9.24 ± 5.05 [a]	6.63 ± 1.02	5.56 ± 2.25	6.72 ± 2.34
S. purpurea (2)	38.88 ± 1.19 [c,d,e]	---	---			
S. decora (1)	19.63 ± 0.57 [a,b,c,d,e]	101.68 ± 2.08 [j,k,l,m,o]	4.28 ± 1.53 [a]	7.83 ± 1.94	8.86 ± 1.61	9.02 ± 3.18
S. decora (2)	48.95 ± 2.49 [d,e]	145.62 ± 9.27 [d,e,f]	5.51 ± 2.69 [a,b]	14.57 ± 5.58	24.16 ± 4.07	25.89 ± 8.73
S. decora (3)	52.39 ± 0.57 [d,e]	38.85 ± 0.88 [w]	5.07 ± 1.41 [f,k,l,m,o]	25.75 ± 8.56	77.50 ± 43.19	110.60± 61.84
S. decora (4)	21.75 ± 0.31 [a,b,c,d,e]	108.97 ± 4.41 [i,j,k]	4.70 ± 0.74 [a]	8.28 ± 1.09	4.83 ± 0.24	4.36 ± 0.44
S .fuscum	104.09 ± 4.05 [g,h,i]	112.49 ± 3.52 [h,i,j]	2.24 ± 1.96 [j,n,o,p]	27.10 ± 3.48	87.23 ± 15.40	127.77 ± 17.67
V. vitis-idaea var *minus*	140.06 ± 6.82 [i]	107.34 ± 3.30 [i,j,k,l]	3.29 ± 0.37 [e,f,g,h,u,j]	31.26 ± 4.52	59.43 ± 0.00	88.91 ± 13.80
V. uliginosum var. *alpinum*	17.93 ± 0.37 [a,b,c,d,e]	128.59 ± 5.92 [f,g,h,i]	7.85 ± 3.45 [a]	10.00 ± 1.12	8.66 ± 1.03	4.67 ± 0.39

Table 2. *Continued*

Scientific name (Label) [1]	DPPH [2]	CD [2]	TBARS [2,3] 0 min	90 min	180 min	240 min
NON-MEDICINAL PLANTS						
A. borealis	109.99 ± 3.73 ^{g,h,i}	106.24 ± 10.96 ^{j,k,l}	-0.17 ± 0.42^{i,k,l,m,n,o}	27.57 ± 3.06	76.36 ± 18.23	114.22 ± 16.98
A. maritima ssp *labradonica*	77.72 ± 2.63 ^{e,f,g}	105.57 ± 9.02 ^{j,k,l,m,n}	2.86 ± 2.63 ^{s,u}	45.3 ± 5.03	146.75 ± 4.29	194.31 ± 12.41
B. grandulosa	22.02 ± 1.06 ^{a,b,c,d,e}	79.60 ± 7.54 ^{p,q,r,s}	-0.45 ± 0.27 ^{a}	3.46 ± 0.29	6.97 ± 1.53	3.14 ± 0.30
C. rodundifolia	118.59 ± 4.20 ^{h,i}	137.86 ± 3.18 ^{e,f,g}	1.09 ± 1.80^{k,p,q}	29.51 ± 3.86	90.84 ± 22.52	140.41 ± 17.03
C. angustifolium	9.11 ± 0.35 ^{a,b,c}	96.12 ± 2.25 ^{j,k,l,m,n,o,p}	0.48 ± 0.85 ^{a}	2.57 ± 0.53	5.75 ± 2.34	2.07 ± 0.44
E. arvense	356.77 ± 13.02 ^{l}	116.89 ± 4.25 ^{g,h,i,j}	2.80 ± 2.11^{m,p,q,r}	39.03 ± 4.99	107.14 ± 4.62	156.46 ± 13.46
H. vulgaris	67.96 ± 0.71 ^{e,f}	130.84 ± 9.26 ^{f,g,h}	0.50±0.87 ^{f,a}	10.15 ± 3.06	38.15 ± 22.83	51.23 ± 35.50
H. peploides ssp *peploides*	206.34 ± 3.20 ^{j}	106.08 ± 2.68 ^{j,k,l,m}	2.22±1.23 ^{t,u}	59.15 ± 6.54	174.44 ± 16.94	209.51 ± 16.04
L. procumbens	30.29 ± 0.89 ^{a,b,c,d,e}	164.57 ± 5.32 ^{b,c,d,e}	-1.76±0.00 ^{a}	8.04 ± 0.56	16.62 ± 7.76	21.31 ± 7.62
M. gale NM	17.60 ± 0.34 ^{a,b,c,d}	98.56 ± 1.03 ^{j,k,l,,o,p}	4.46±2.30 ^{a}	13.32 ± 7.44	15.02 ± 4.08	12.39 ± 4.66
R. rugosum	320.95 ± 6.17 ^{k}	133.60 ± 5.72 ^{f,g,h}	0.08 ± 0.88 ^{p,s,t}	39.92 ± 4.37	130.29 ± 6.34	177.09 ±13.19
R. Chameamorus	28.93 ± 0.60 ^{c,d,e}	78.62 ± 2.61 ^{p,q,r,s}	6.40 ± 5.10 ^{a}	15.71 ± 4.15	17.70 ± 6.13	8.34 ± 1.62
S. arctophyla	19.10 ± 0.56 ^{a,b,c,d,e}	49.72 ± 1.59 ^{v,w}	2.27 ± 1.06 ^{a}	4.95 ± 0.67	6.50 ± 1.31	3.67 ± 2.00
S. paschale	495.51 ± 34.94 ^{m}	141.16 ± 3.63 ^{e,f}	-0.21 ± 0.79 ^{l,p,q}	24.95 ± 1.02	87.10 ± 18.05	142.59 ± 4.84
S .russowii	70.06 ± 2.19 ^{e,f}	139.98 ± 1.90 ^{e,f}	0.09 ± 0.88^{c,f,g,h,i,j}	20.32 ± 4.70	56.46 ± 15.12	73.23 ± 19.47
T. huronense var. *bifarium*	77.33 ± 1.53 ^{e,f,g}	64.66 ± 10.80 ^{r,s,t,u,v}	-1.19 ± 0.00^{h,k,l,m,n,o}	23.18 ± 4.96	71.73 ± 19.23	115.59 ± 27.34

[1] See Table 1 for the label signification.
[2] Means with the same letters within an assay are not significantly different between plant species determined by Fisher analysis ($P < 0.05$).
[3] Statistical results for the repeated measure analysis between species. Statistical results are not shown within each time interval.

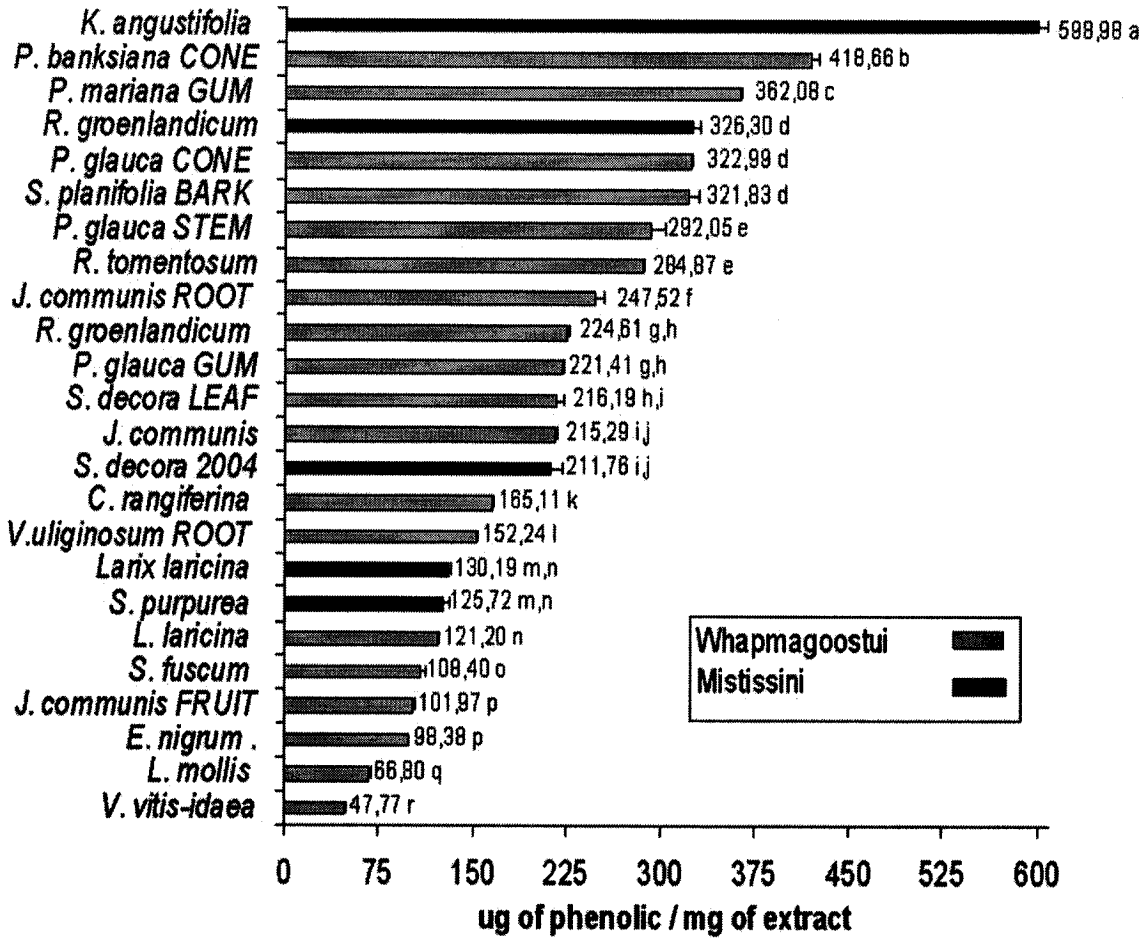

Figure 1.

Total water-soluble phenolic content of twenty-four medicinal species used in both communities (Mistissini and Whapmagoostui). Values are expressed in μg of phenolic / mg of extract. The standard curve is based on quercetin. Bars represent means ± SEM of n = 5. Different letters show significant differences between adjacent species as determinated by Fisher analysis ($P < 0.05$).

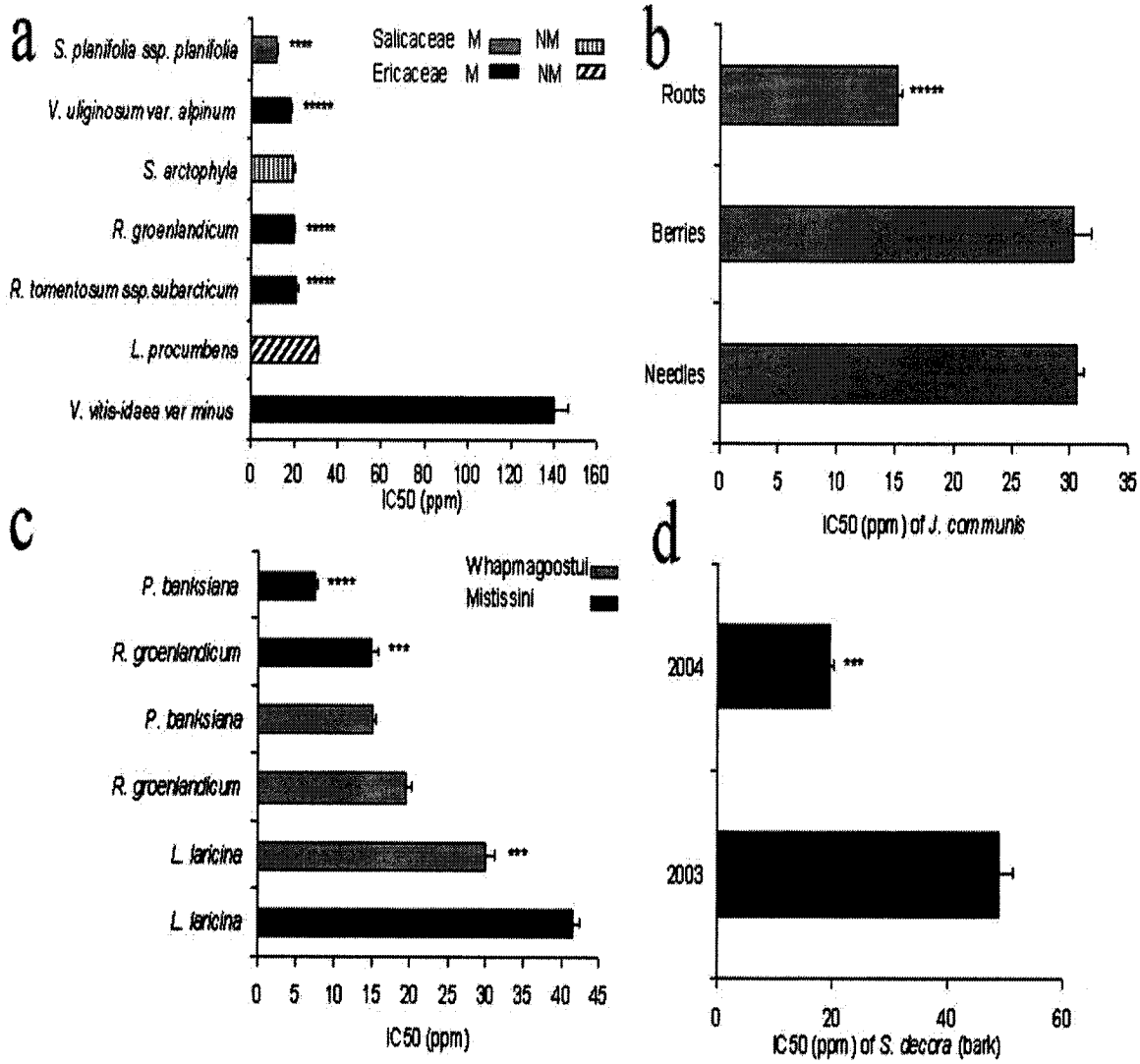

Figure 2.

Free radical scavenging potential of ethanolic plant extracts measured by the 1,1-diphenyl-2-pycryl-hydrozyl (DPPH) assay. Determined from the linear portion of the dose-response curve obtained from ascorbic acid, IC_{50} is the concentration needed to obtain half of total inhibition by ascorbic acid. Plants with low concentrations correspond to relatively high antioxidant activity. Bars represent means ± SEM of at least three independent assays perform in duplicate. Different groups of samples are compared as follows: a) the same families where plant species are medicinal (M) or not (NM); b) different parts used from *Juniperus communis;* c) the same plants of both studied communities (Whapmagoostui and Mistissini); and d) different years from *Sorbus decora.* Statistical tests applied were Mann Whitney (1), Kruskal-Wallis (2) and Tukey (3) for a) Salicaceae (1), Ericaceae (2) b) *Juniperus communis* (3) c) both studied communites (1) and d) *S. decora* (1). Significant differences between groups compared are represented by ***** 0.000; ****0.001; ***0.01.

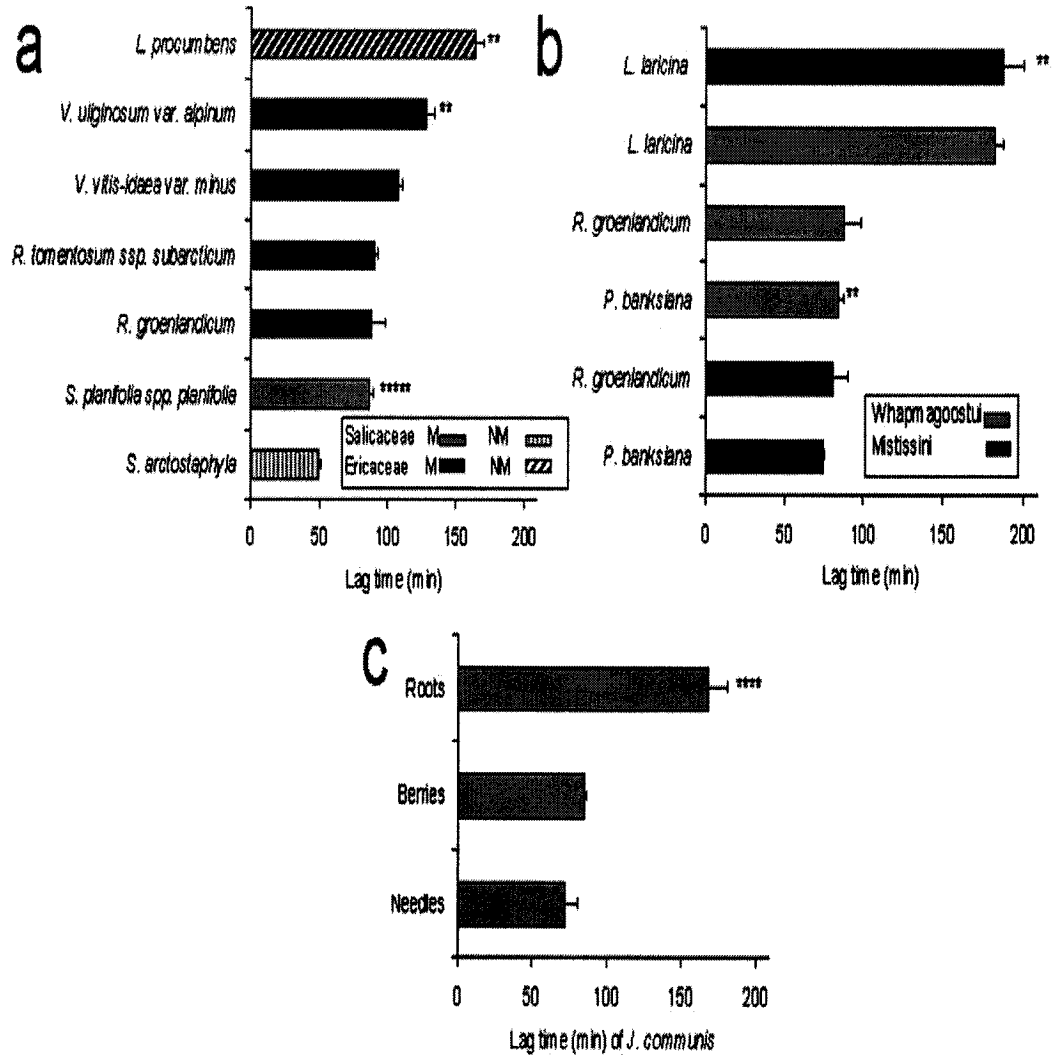

Figure 3.

Inhibition of conjugated dienes formation expressed in lag time (min) among plant extracts (5 ppm). The lag time represents the beginning of LDL oxidation with 15 μM $CuSO_4$ calculated from A_{234nm} taken in five min intervals. A longer lag time corresponds to a high antioxidant activity. Bars represent means ± SEM of duplicate samples of three experiments. Diverse groups of samples are represented to be compared as follows: a) the same families where plant species are medicinal (M) or not (NM); b) the same plants of both studied communites (Whapmagoostui and Mistissini); and c) different parts used from *Juniperus communis.* Statistical tests applied were Mann Whitney (1), Kruskal-Wallis (2) and Tukey (3) for: a) Salicaceae (1), Ericaceae (2) b) both studied communites (1) and c) *Juniperus communis* (3). Significant differences between groups compared are represented by ***** 0.000; ****0.001; ** 0.05.

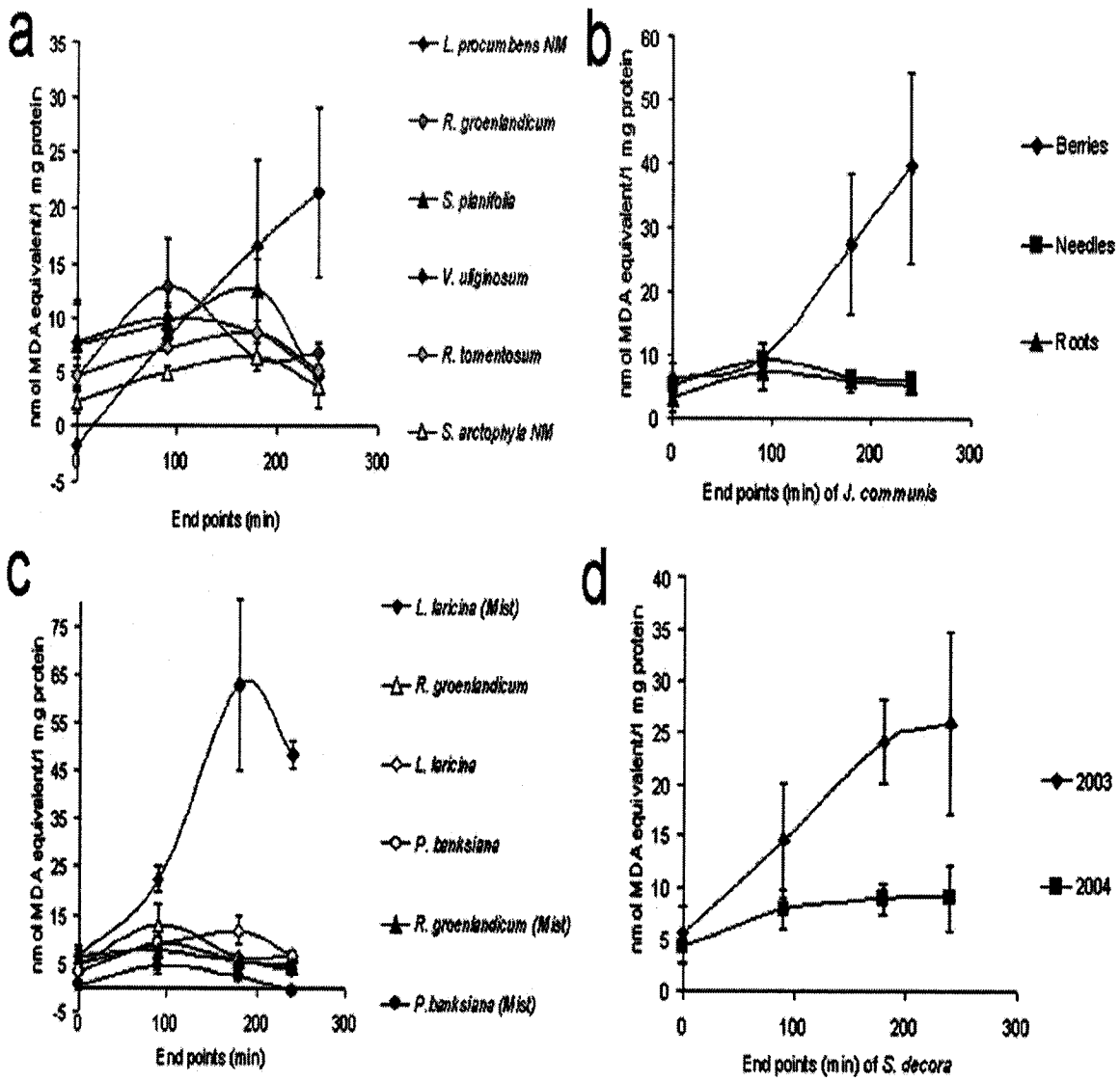

Figure 4.

Thiobarbituric acid reactive substances (TBARS) formation of plant extracts (5ppm) incubated with 15 μM $CuSO_4$ and 100 μg LDL, through four end points; 0-90-180-240 min. From the fluorometer values measured at excitation wavelength 510 nm / emission wavelength 553 nm, results were expressed as nmol MDA equivalent / mg LDL protein. Each value was found by regression analysis based on MDA standard curve. Higher antioxidant activity is represented with lower MDA production. Bars represent means ± SEM of duplicate samples of three independent experiments. Diverse groups of samples are represented to be compared as follows: a) the same families whereas plant species are medicinal (blank) or not (NM); b) different parts used from *Juniperus communis;* c) the same plants of both studied communites [Whapmagoostui (blank) and Mistissini (Mist.)]; and d) different years from *Sorbus decora* ($p = 0.01$).

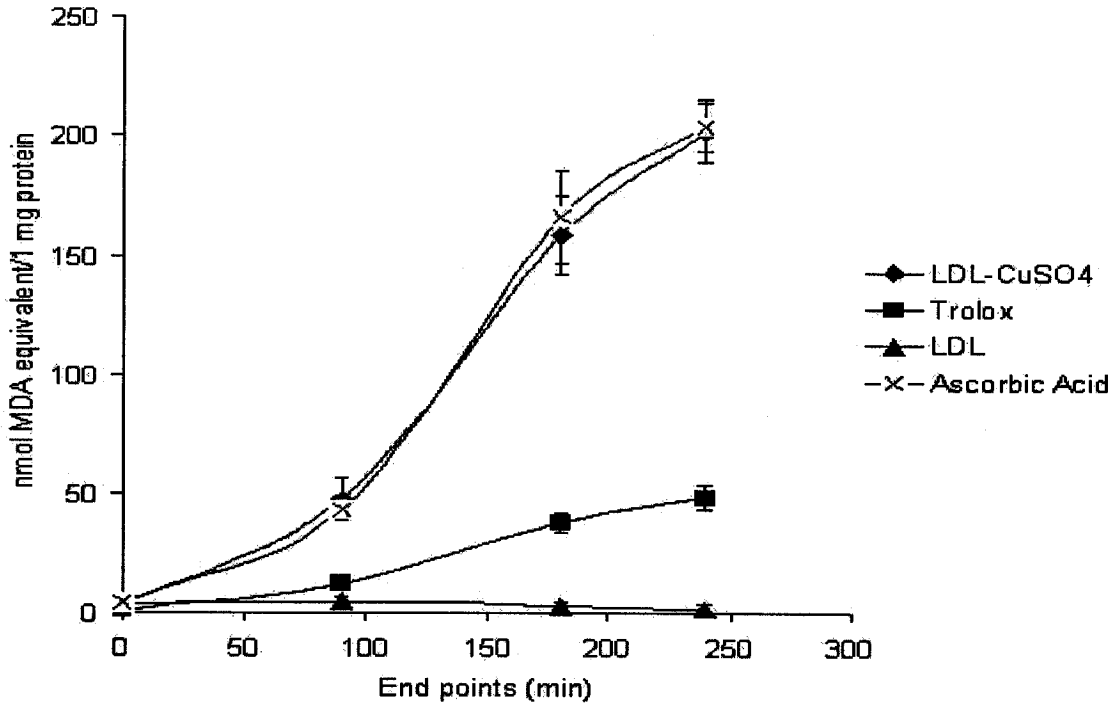

Figure 5.

Thiobarbituric acid reactive substances (TBARS) formation of ascorbic acid (28.39μM) and Trolox® (19.98μM) compared with the control (LDL-$CuSO_4$) incubated with 15 μM $CuSO_4$ and 100 μg LDL, through four end points; 0-90-180-240 min. From the fluorometer values measured at excitation wavelength 510 nm / emission wavelength 553 nm, results were expressed as nmol MDA equivalent / mg LDL protein. Each value was found by regression analysis based on MDA standard curve. Higher antioxidant activity is represented with lower MDA production. Bars represent means ± SEM of duplicate samples of three independent experiments.

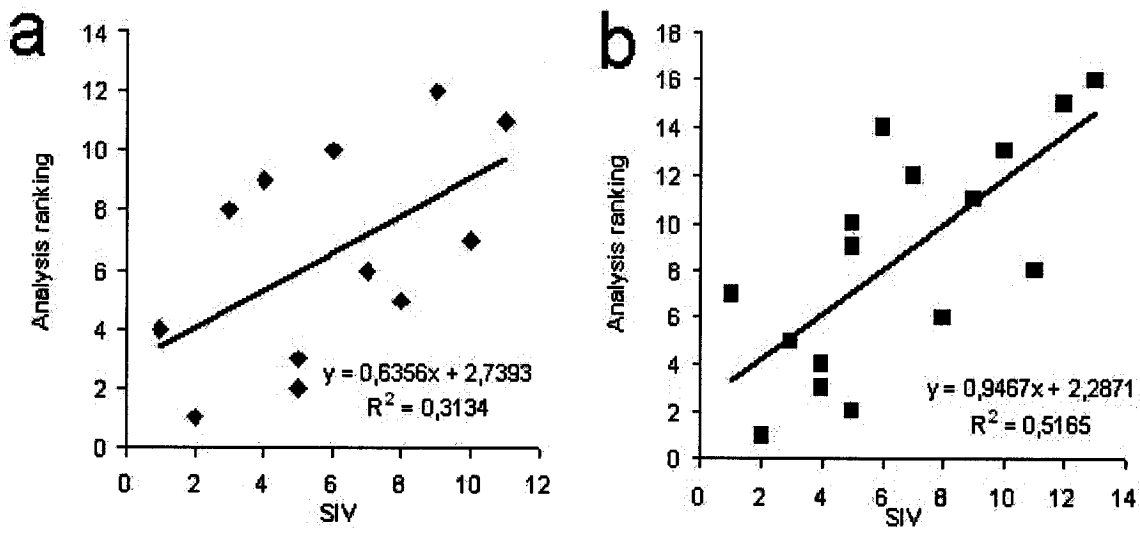

Figure 6.

Spearman's correlations test between analysis (three bioassays) and ethnobotanical survey (Syndromic Importance Value (SIV)). Ethnobotanical data are correlated with the antioxidant activity, where the ranking of each plant species tend to be similar. Correlation coefficients on medicinal plants from a) Mistissini is $r = 0.3134$ ($p = 0.058$) and b) Whapmagoostui is $r = 0.5165$ ($p = 0.001$).

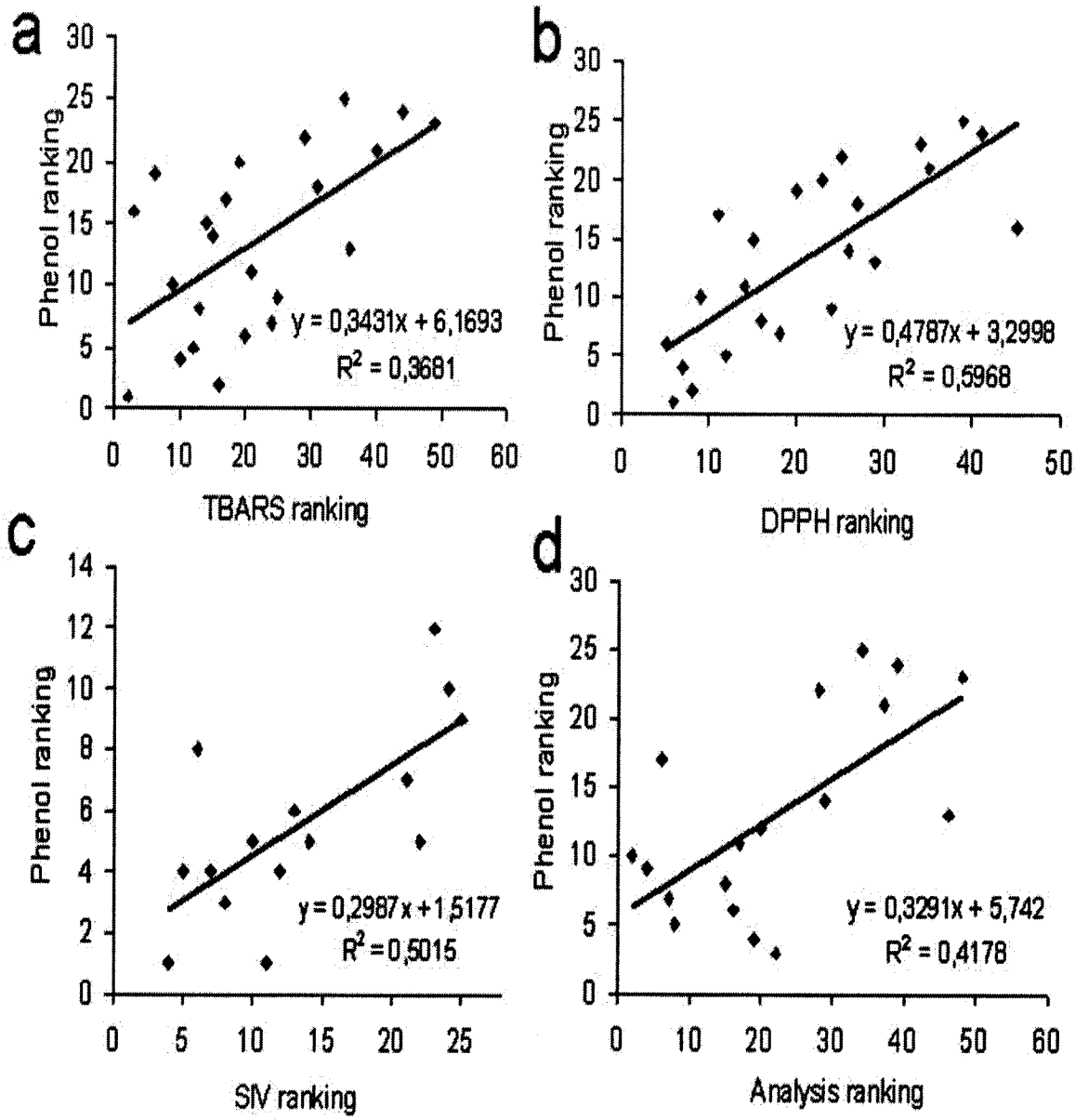

Figure 7.

The Spearman's correlation test illustrates positive relations between the ranking of water-soluble phenol content obtained from medicinal plants with the ranking of a) thiobarbituric acid reactive substances (TBARS) r = 0.3681 (p = 0.002); b) 1,1-diphenyl-2-pycryl-hydrozyl (DPPH) r = 0.5968 (p = 0.00015); c) ethnobotanical data (Syndromic Importance Value (SIV)) r = 0.5015 (p = 0.003) (Fraser *et al.* Manuscript I); and d) bioassays r = 0.4178 (p = 0.003).

7.4. Discussion

7.4.1. Antioxidant activity of Cree Eeyou Istchee traditional medicine

Among the three antioxidant bioassays (DPPH, CD and TBARS), medicinal plants from the two Cree communities in Québec confirmed the antioxidant activity of TM from the boreal forest as demonstrated by McCune and Johns (2002). Some TMs have presented a greater degree of activity than ascorbic acid and Trolox®, such as extracts from those found in Pinaceae and Ericaceae. Identification of important TMs that treat T2D symptoms is validated when evaluated in bioassays, ethnobotanical data and phenolic content. Plant-derived antioxidants other than phenolics listed in Appendix 5 could explain the high amount of antioxidant activity in the bioassays within studied plants. As expected, Elders and Healers selected plant species with antioxidant abundance, such as phenolics, to treat T2D symptoms.

51.92 % of plants identified by Cree Elders and Healers for their medicinal properties had statistically similar or better radical scavenger activities than vitamin C, while 63.83 % prolong CD formation and 95.92 % limit MDA production equally well as ascorbic acid. McCune and Johns (2002) found 14 % of their samples similar to vitamin C in free radical scavenging. Since vitamin C is affected by oxidation and heat, the preparation of plants as a tea decoction by Elders and Healers, likely increases the quantity of this vitamin in the beverage (Berkes and Farkas 1978).

The validation of medicinal uses by decoction among communities could be an effective way of promoting vitamin C consumption, thereby preventing T2D symptoms. However, as mentioned earlier, this vitamin can be a pro-oxidant under a certain critical concentration (Otero *et al.* 1997). This was observed along in the TBARS experiment, where ascorbic acid produced a high quantitiy of TBARS comparable to the LDL-control (Fig. 5). Owen (2000) and Patel *et al.* (1997) have also observed oxidant activity of ascorbic acid. The high concentration used would explain the pro-oxidant activity. Eventually, it should be measured in more realistic *in vivo* conditions and with a lower concentration.

In addition, 40.43 % of medicinal plants in the CD assay and 73.47 % of medicinal plants by TBARS have shown similar or better activity than Trolox®, a vitamin E analog. This vitamin is a lipid-soluble and a well known antioxidant (Pratt 1992) and scavenger (Maxwell 1995). Similarly, McCune and Johns (2002) found that between 23 % and 60 % of medicinal plants were higher or comparable with the Trolox® values depending on the experiment conditions.

7.4.1.1. DPPH scavenging activity

Based on the reduction of a DPPH radical at 517 nm, 72 % of plant samples of Whapmagoostui, Mistissini and samples of non-medicinal plants had the ability to donate hydrogen below 50 ppm. Therefore, they were effective scavengers and potentially good antioxidants. *Pinus banksiana* and *Chamerion angustifolium* exhibited the highest scavenging activity, where values obtained tended to be similar to those found in studies by Zulaica-Villogomez *et al.* (2005) and Myagmar and Aniya (2000) studies.

Four plants studied by McCune and Johns (2002) demonstrated comparable results to the present study, specifically *Kalmia angustifolia* (11.4 ± 2.6 ppm), *Juniperus communis* (11.8 ± 2.3 ppm), *Rhododendron groenlandicum* (21.9 ± 1.8 ppm), and *Abies balsamea* (22.2 ± 1.1 ppm). The reference materials used, which were vitamin C and flavonoids such as quercetin, catechin, epicatechin, are quenchers of the free radical, ROS (Yokozawa *et al.* 1998; Owen and Johns 2002; Acuna *et al.* 2002). The results for them are comparable to the literature (Kolayli *et al.* 2003; Ursini *et al.* 1994; Choi 2002; McCune and Johns 2002).

7.4.1.2. CD lipid peroxidation assay

A combination of LDL oxidation assay with DPPH assay is useful for assessing the antioxidant potential of plants (Katsube *et al.* 2004). Oxidized LDL is implicated in artherosclerosis development and therefore is linked to the causes of T2D complications (Baynes and Thorpe 2000; Levy *et al.* 2000). Thus medicinal plants have been studied with CD and TBARS, two conventional lipid peroxidation bioassays. Antioxidants were shown to retard oxidation bioproducts formation during the propagation phase (Esterbauer *et al.* 1990). Within the CD assay, ascorbic acid and Trolox® showed long lag

time, 108.26 ± 3.13 min and 130.59 ± 9.84 min, comparable to those found in the studies of Yen and Hsieh (2002) and Mathiesen *et al.* (1996a, b), respectively. In showing comparable lag times to these reference materials, medicinal plants demonstrated effective antioxidant potential.

Larix laricina identified and isolated from both Cree communities had the highest lag times. The cambium or inner bark of tamarack used is a fresh and young structure. Meristematic cells are produced constantly and could possibly contain a higher quantity of secondary metabolites. For example, woody tissues contain tannins (Owen 2000).

7.4.1.3. TBARS lipid peroxidation assay

Trolox® showed similar production of TBARS to Vaya *et al.* (1997). In comparison with Trolox®, 59.18 % of plants sampled exhibited lower formation of MDA, therefore they showing better antioxidant activity than Trolox®. However, although ascorbic acid and Trolox® have been measured in TBARS assays (Otero *et al.* 1997; Vaya *et al.* 1997; Leung *et al.* 2001; Yen and Hsieh 2002), Canadian plants have been less studied in this lipid peroxidation assay than in the CD assay. Indeed, McCune and Johns (2002) are the only researchers who have described antioxidant activity among TM that treat T2D symptoms used by North American Indigenous people. However, comparable TBARS production has been measured by Jones *et al.* (1998) in the oil of juniper berries in rats.

It was noted that the production of TBARS decreased at 180 min for some plant samples. This is the case in *Larix laricina* (Mist.) illustrated in Figure 4. Also, *Picea glauca*-stem showed the strongest decrease from 90 min to 240 min. In previous studies, a decrease of TBARS production was also observed for ß-carotene (Lukaszewicz *et al.* 2004), soybean (Romero *et al.* 2004) and others (Leung *et al.* 2001). In specific observations of the TBARS assay, Safari and Sheikh (2003) have shown that LDL exposed to flavonoids *in vitro* reduced oxidizability, especially quercetin. Flavonoids contained in some studied plants that strongly inhibited TBARS formation induce a decrease in endpoints such as those for *Picea glauca, Salix planifolia, Vaccinium uliginosum* and *Sorbus decora.* The TBARS production decline could be due to the action of those flavonoids on the LDL molecule at a certain time.

Also, Esterbauer *et al.* (1987) has suggested that the TBARS assay is not specific for malonaldehyde, since many other compounds also give the pink pigment under these assay conditions. Those potential compounds could have been formed along the end points and could interfere with the fluorometer reading, since LDL is an unstable molecule in comparison with MDA that is a more stable end product of lipid peroxidation (Petlevski *et al.* 2003).

7.4.1.4. Water-soluble phenolic content

Water-soluble phenolic compounds are high in almost all the plants species studied (Proteggente *et al.* 2003). Therefore, this complementary compositional analysis confirmed the antioxidant capacity in bioassays, for example in phenolics. Blokhina *et al.* (1999) has mentioned that phenolic compounds involve a hydrogen peroxide scavenging cascade in plant cells and act as active antioxidants. The high phenolic content was confirmed among medicinal extracts from both communities in this study, and were shown to contain between 47.7 and 599.0 µg of phenolic / mg of extract, a value higher than most fruits and vegetables (Proteggente *et al.* 2003). Since *Kalmia angustifolia* presented higher phenolic content, it is possible that this is due to the presence of phenolic allelochemicals that are phytotoxic (Mallik 2003) or tannins (Marles 2001). According to the participants who took part in this study, this plant species is toxic and dangerous (Fraser *et al.* Manuscript I). Indeed, there are toxic diterpenoids isolated by Burke *et al.* (1989) and toxic alkaloids (Mancini and Edwards 1979).

Using a different method, Owen and Johns (1999) measured higher content for phenol in *Larix laricina,* but obtained similar results for *Rhododendron* spp. The difference between tamarack results could be due to the extraction procedure, which affected phenol content (Cowan 1999). Alternatively, this could be due to different environmental parameters, such as greater exposure to sunlight, high altitude, and herbivory that results in an increased concentration of phenolics in plants of the same species (Ernst *et al.* 1991). Or, this could be due to plant-derived antioxidants that interfered in the Folin-Ciocalteu method (Singleton and Rossi 1965). Another observation illustrates that phenolics are not equally widespread within a whole plant. *Vaccinium uliginosum*

demonstrated higher phenol content in roots (152.2 µg of phenolic / mg of extracts) than in berries as Kahkonen *et al.* (1999) has measured (28.7 mg of gallic acid eq. / g of extracts). These could be anthocyanins and polyphenolics compounds that are widespread among blueberries (Lee *et al.* 2004). As mentioned by participants, berries are eaten while roots are used for medicinal purposes. Thus, according to participants each organ used on a specific species is chosen for an appropriate use or application.

7.4.1.5. Supplementation

To supplement the present study, LDL, in the presence (results not shown) and absence of glucose (Table 2) was added to $CuSO_4$ in a CD bioassay in order to test the effects of glucose on the lipid peroxidation with LDL. Solutions with glucose had lower lag time than solutions without glucose. Thus, glucose reacted as an oxidant on the LDL molecule, due to the early formation of oxidation products. As Sobal *et al.* (2000) have shown, glycated LDL is more prone to oxidation than native LDL. The CD assay showed that glucose affected the LDL molecule, thereby suggesting the role of advanced glycolysation products in T2D complications (Cerami *et al.* 1988). Medicinal plants have demonstrated, even in presence of glucose, longer lag time than non-medicinal plants. By chain breaking antioxidants in the medicinal plants, LDL is more protected against glucose and other oxidants, which have the potential to defer T2D development.

7.4.2. Antioxidant activity evaluation among plant categories

7.4.2.1. Medicinal and non-medicinal plants

Antidiabetic plant species identified by the Cree show higher antioxidant potential than the majority of the non-medicinal plants samples. A similar study has shown that antidiabetic plants have higher antioxidant potential than commercial food products due to the presence of tannins (catechin), flavonoids and vitamin E (McCune and Johns 2002). Furthermore, Hoffman *et al.* (1967) has reported that eastern Arctic plants such as *Leymus mollis, Empetrum nigrum, Chamerion angustifolium, Rubus chamemorus, Salix planifolia, Salix arctophila* and *Vaccinium vitis-idaea,* have a high content of either ascorbic acid, β-carotene, or both. These include medicinal and non-medicinal plants. In the assays used in this study, it was shown that individual non-medicinal plants have better antioxidant potential than the majority of chosen medicinal plants, specifically

Chamerion angustifolium (DPPH; TBARS), *Myrica gale* (DPPH), *Betula glandulosa* (DPPH; TBARS), *Loiseleuria procumbems* (CD; TBARS) and *Salix arctophyla* (DPPH) which are known for their plant-derived antioxidants (Hoffman *et al.* 1967; Glasby 1991; Kuhnlein and Turner 1991; Mathiesen *et al.* 1995, 1996a, b and 1997; PDR for Herbal Medicine 1998; Powell and Raffa 1999a, b; Cuendet *et al.* 2000; Kiss *et al.* 2004). Nonetheless, the overall difference indicates that Elders and Healers have selected effective medicinal plants with antioxidant activity. Moreover, they have other potentially antioxidant species available in their communities. Further research could verify this information in cooperation with Elders and Healers, as well as gather more information going beyond the T2D-specific interview questions regarding their perception of these plants (Fraser *et al.* Manuscript I). It possible that that these plant species have further medicinal values.

7.4.2.2. Whapmagoostui and Mistissini extracts

The higher antioxidant potential in the Whapmagoostui medicinal plants compared to those in the southern community of Mistissini could be due to an ecological gradient, whereby plants are exposed to different environmental pressures (Ehrlich and Raven 1964; Berenbaum 1983). The aridity in the region of Whapmagoostui and the physical characteristics, such as its coastal and northern location, could induce higher antioxidant production in plants than those in the boreal forest region of Mistissini. Indeed, Arctic adapted plants, such as those at Whapmagoostui, produce more secondary metabolites for their defence than similar plants situated in boreal forests (Savile 1972; Dalton 1995).

Larix laricina (Figs. 2c and 4c), *Rhododendron groenlandicum* (Fig. 3b) and *Pinus banksiana* (Fig. 3b) from Whapmagoostui have better scavenging and antioxidant activity. Differences in the fresh initial material gathered initally by diverse collectors in Mistissini and at Whapmagoostui could account for some of the differences related to antioxidant activity. For instance, the collection of cones at different stages of maturity in Mistissini was probably the case for *Pinus banksiana*, where extracts from Whapmagoostui of young cones were collected. Supporting this possible difference is a study by Zulaica-Villogomez *et al.* (2005), which showed better activity among young pinecones than old.

7.4.2.3. Parts used

A few studies compare antioxidant properties on different plant parts from the same species (Fediuk *et al.* 2002; Angioni *et al.* 2003; Zulaica-Villogomez *et al.* 2005), as well as on different species for the same parts (Hakkinen 1999). It should be noted that Elders and Healers at Whapmagoostui used several tissues from *Picea glauca*-gum-needle-cone, *Juniperus communis*-berries-root-needle and *Sorbus decora*-stem-leave (Fraser *et al.* Manuscript I). Antioxidants are different from one structure to another because of environmental pressures from insects or herbivores (Ernst *et al.* 1991). This can be seen, for example, in the results found in the phenolic evaluation. However, activity tends to be similar for needles and berries on *Juniperus communis* (Figs. 2b and 3c) where roots showed more antioxidant activity as well as *Vaccinium uligonosum* (Table 2). Shahmir *et al.* (2003) have described 41 and 27 components contained in the oil of juniper needles and berries.

7.4.2.4. Time of collection

The time of collection appears to affect the antioxidant capacity in the case of *Sorbus decora,* where extracts from Mistissini presented better antioxidant activity in 2004 than in 2003 (Figs. 2d and 4d). However, this could have been the result of deterioration of certain compounds since the initial period of collection (Cowan 1999). For example, phenolic levels are higher in recent extracts (Ernst *et al.* 1991). In this study, Soxtec extraction was applied to samples from 2004, in order to isolate different components, than from 2003 samples which were extracted using another method (Spoor *et al.* 2006). Therefore, the time of collection and/or the extraction method used could potentially modify antioxidant content.

Antioxidant content, related to compounds such as phenolics, varies with season (Conner *et al.* 2002). Arctic plants studied previously were collected in August, the most advantagous time of year in the cycles of the growing season, according to the study of Hoffman *et al.* (1967). Czeczuga (1994) has also shown that phenolic levels may change according to the immediate plant environment, including being situated in shade or sunlight. In this sense, Elders and Healers have their own specific methods of collecting medicinal plants. For example, Elders and Healers collect mature fruits of *Vaccinium*

vitis-idaea in spring when their properties are fully medicinal. However, in this study immature berries of *Vaccinium vitis-idaea* were collected in August. Therefore results demonstrated low scavenging activity, low phenolic content (Figs. 1 and 2a) and also an exponential increase of TBARS reaching 89 nmol at 240 min (Table 2). Future studies could benefit from following a different plant collection timeline in order to take advantage of these seasonal factors and the changing phenolic content during periods of growth.

7.4.3. Correlation among antioxidant activity measures

Rank values, given to each sample within three bioassays instead of comparing raw data together as previous studies (Javanmardia *et al.* 2003; Proteggente *et al.* 2003; Cai *et al.* 2004; Katsube *et al.* 2004), demonstrated positive correlations between DPPH and TBARS ($r = 0.7811$; $p = 0.0000$). However, CD showed negative correlations with DPPH ($r = 0.245$; $p = 0.0005$) and TBARS ($r = 0.2223$; $p = 0.0009$). Similar plants that contained strong antioxidant activity in both TBARS and DPPH were the following: *Pinus banksiana*-cone (Mist), *Picea mariana*-cone (Mist), *Salix planifolia* and *Rhododendron groenlandicum* (Mist-Whap). By contrast, *Salix arctophyla, Alnus incana* ssp. *rugosa, Saracenia purpurea* and *Pinus banksiana* differed between CD with DPPH (Figs. 2c, 3b) and TBARS (Table 2). In addition, while Katsube *et al.* (2004) have evaluated correlations of antioxidant activity and phenolic content with raw data, this present project used a comparable approach rank test based on the centered reduced method. The results from three bioassays, where units are not comparable, were standardized on unique rank value for each sample. Therefore, comparisons using normalized ranks instead of raw data allowed analyzing comparable correlations. By using this unique rank approach, positive correlations were observed with phenolic results and DPPH $r = 0.5968$ ($p = 0.000015$) and with TBARS $r = 0.3681$ ($p = 0.0020$) (Figs. 7a, b).

CD had very low correlation with phenolic results. This correlation was not shown. A few studies have compared rankings from two tests together, and have shown low and / or negative correlations between CD and TBARS (Chajès *et al.* 1996; Diwadkar *et al.* 1999). In general the literature does not compare those two bioassays together; rather, it

considers them as independent results. Indeed, the bioassays measure different parameters and products released, where secondary compounds could react differently with reagent and experimental conditions. Katsube *et al.* (2004) has suggested that differences could be a consequence of the affinity of antioxidants to LDL in regard to chelating agents such as phenolics, in which they combine their metal molecule (s) with an organic compound causing a reaction. This is probably the case for the CD assay, where certain molecules reacted differently or were formed over time and read at 234nm. In regard to the secondary metabolites present, in the presence of glucose, flavonoids inhibit the antioxidant activity. In all, the study demonstrated that DPPH and TBARS bioassays were acceptable for evaluating antioxidant capacity in extracts with phenolics.

Positive correlations between the bioassays and the ethnobotanical survey validate the selection of medicinal plants among the Cree communities as the more effective plants in terms of antioxidant activity (Fig. 6). The unknown antioxidants contained in the plant extracts studies may have a role in alleviating symptoms associated with T2D. Indeed, *Larix laricina* is frequently used in both communities to treat symptoms of diabetes (Fraser *et al.* Manuscript I), and this plant species has shown the highest antioxidant activity among three bioassays. McCune (1999) also identified tamarack as an important TM in the treatment of T2D symptoms and as an antioxidant. For medicinal extracts of *Empetrum nigrum, Cladonia rangiferina* and *Gaultheria hispidula* low SIV (Fraser *et al.* Manuscript I) likewise correlated with the bioassay rank (Table 1).

Elders and Healers do not select remedies at random, but rather specific species and even precise plant parts. For example, *S. decora*-stem was more selected than the leaves, while the leaf extract demonstrated lower antioxidant activity than the stem extract among the three bioassays (Table 2). In addition, since non-medicinal plants such as *Stereocaulon paschale*, *Armenia maritima, Equiseum arvense* and *Rhytidium rugosum* were not used by Elders and Healers, as expected the majority of these extracts ranked lower among bioassays, in comparison with medicinal plants placed on the first twenty-five rank (Table 1). However *Loiseleuria procumbens,* a non-medicinal Ericaceae plant showed effective antioxidant activity as well as phenolic content (256.7 ± 3.9 µg of phenolic / mg of

extract). This is consistent with secondary metabolite content in this family as exemplified by *Rhododendron groenlandicum, R. tomentosum, Vaccinium uliginosum* and *V. vitis-idaea.* Many of these compounds extracts have hyperglycaemic activity (Marles and Farnsworth 1995, see Appendix 5).

Usually, small procumbent plants, like *Loiseleuria procumbens*, are not selected as medicinal among the Cree (Elders and Healers, *pers. comm.*). It is arguable that knowledge of the antioxidants or healing properties in these plant species as potential medicine has not yet been realised. Although Elders and Healers who are respected within their communities teach Cree medicine to the younger generation and throughout history have selected the most important and useful plants, it is possible that there are still plants unknown to these communities despite their antioxidant potential. Or similarly, it is possible that knowledge of the medicinal power of certain plants has changed over many generations of passing down traditional knowledge to Elders and Healers.

For this project water-soluble methods were chosen for phenolic determination, since Elders and Healers used medicinal plants by decoction, in order to make phenolics results comparable with ethnobotanical data (SIV). Although the extractions for bioassays were based on an organic solvent (EtOH) to maximize the sensibility of measurements, these results remain comparable with phenolics and SIV results. Indeed water-soluble phenolic content correlated strongly with the ethnobotanical survey ($r = 0.5015$; $p = 0.003$) and the bioassays ($r = 0.4178$; $p = 0.003$). In other words, the *r* coefficients of Figures 7a and 7b indicated that the ethnobotanical survey predicted phenolic content in 50.15 %, and bioassays predicted phenolic content in 41.78 %. Similarly, Katsube *et al.* (2004) has reported significant correlations between DPPH bioassay and phenolic content. Also, Fraser *et al.* (Manuscript I) has suggested for a group of plants clustered in the dendrogram of Whapmagoostui that there is a correspondance with high phenol content with *Rhododendron groenlandicum, R. tomentosum, Picea glauca* and *P. mariana,* as well with low phenol content for *Vaccinium vitis-idaea* and *Empetrum nigrum.* These species that treat the same T2D symptoms due to the clustering could be verified by comparison with phenolics results. Thus, previous dendrograms obtained could illustrate

clustered groups of plants that could correspond to the antioxidant category such as phenolics.

In addition, plant-derived antioxidants other than phenolics could be responsible of antioxidant capacity in bioassays such as listed in Appendix 5. They could be predicted by the ethnobotanical survey in 49.85 % (100 - 50.15 in Fig. 7a) and bioassay in 58.55 % (100 - 41.78 in Fig. 7b) (Javanmardia *et al.* 2003). This is probably the case for *Larix laricina, Sarracenia purpurea* and *Sorbus decora* and a few others that demonstrate high SIV and low phenol rank. In opposition to this, other extracts have shown high phenolic quantity with low SIV, which is the case of *Kalmia angustifolia* and *Pinus banksiana.* With an inland distribution, these particular plant species are less accessible and therefore used with less frequency by the Elders and Healers from Whapmagoostui despite the plant-derived antioxidants they contain (Fraser *et al.* Manuscript I). Further analysis, such as by High-Performance Liquid Chromatography (HPLC), could be used to determine exactly which specific compounds, such as phenolic acids, tannins, coumarins and lignans, quinones, flavonoids, stilbenes and curcuminoids, as shown by Lee *et al.* (2004) and Cai *et al.* (2004), are present in these extracts.

In general, medicinal plants shown to be high in plant-derived antioxidants were selected in the Cree medicine used by the Cree communities. This is the case for Pinaceae and Ericaceae, which has shown, overall, to have the highest phenolic content, as well as for antioxidant activity, where 14 extracts are among the twenty-five highest ranked (Figs. 2a and 3a; Table 1). These plant families are known to be rich in these compounds, specifically flavonoids and phenolic acids (Wardle *et al.* 1998; Mallik 2003). *Kalmia angustifolia, Picea banksiana, Picea* spp., *Rhododendron groenlandicum* with highest phenolic content (Forest and Legault 1977; Larsen 1980; Richardson 1998) and *Larix laricina* are widespread species distributed along the boreal forest in Northern territories of Québec. Elders and Healers have selected widespread antidiabetic species in vegetation ecosystems and those medicinal plants have shown antioxidant abundance and/or demonstrated high plant-derived antioxidants, as in phenols.

7.5. Conclusions

Most of the TM used by the Cree Nation of Eeyou Istchee to treat T2D symptoms showed antioxidant activity greater than that of non-medicinal plants and standard antioxidants, such as ascorbic acid (Vitamin C) and Trolox®. This evidence supports the beneficial effects of Cree TM in the prevention of T2D and its complications. As McCune and Johns (2002) have suggested, the use of TM practiced traditionally by the Cree and individuals in this community today may represent a major contribution to understanding the potential of antioxidants in treating symptoms of T2D. It was also demonstrated that ethnobotanical data, bioassays results and phenolic content were correlated, as suggested from the different rankings of plants compared in this study. From this preliminary screening study, medicinal plants with high antioxidant activity and rank also demonstrated a strong correspondence to existing Cree ethnobotanical information (Leduc *et al.* 2006; Fraser *et al.* Manuscript I). Therefore, these plants used in TM are candidates for further *in vitro* and *in vivo* studies as initiated by Grandi (2006) and Spoor *et al.* (2006) with Mistissini medicinal plants, and ultimately for testing in clinical trials to prevent T2D. Therefore, a primilary list of TM would be *Juniperus communis, Kalmia angustifolia, Larix laricina, Picea glauca, Sorbus decora, Rhododendron groenlandicum* and *R. tomentosum.*

8.0. General Conclusions

This is the first report on the TM used to treat T2D symptoms of the Cree of Eeyou Istchee at Whapmagoostui, a coastal community. Although Cree medicines have been reported among different communities in Canada (Holmes 1884; Strath 1903; Leighton 1985; Marshall *et al.* 1989; Zieba 1992; Siegfried 1994; Leduc *et al.* 2006), the ethnobotanical research here has succeeded in recording new findings about traditional knowledge in relation to the treatment of T2D symptoms. Specifically, *Cladonia rangiferina, Empetrum nigrum, Juniperus communis, Leymus mollis, Sphagnum. fuscum, Rhododendron tomentosum* and *Vaccinium vitis-idaea* have been added to the existing data on Cree medicine from Mistissini. *Larix laricina, Rhododendron groenlandicum* and *R. tomentosum* were also recognized as important Cree medicines because they are widely used and have also been mentioned for the treatment of many symptoms. Futhermore, and also equally important, is new evidence validating the traditional knowledge of Cree Elders and Healers from Whapmagoostui through a more thorough scientific analysis of their traditional practices. Working in harmony with the Cree and emulating their traditional bush skills within ethnobotanical studies has also included the invaluable participation of these knowledgeable Elders and Healers. Moreover, this study has shown that traditional Cree medicine has conserved extensive knowledge of plants for their treatment of symptoms related to T2D, and for their healing properties.

This project primarily compared traditional knowledge of antidiabetic plants between different Cree of Eeyou Istchee communities. Although Leduc *et al.* (2006) have compared their data with Cree literature in Canada, this study expanded the use of quantitative ethnobotany carried out in Cree communities. For example, consensus test was introduced within the field of ethnobotany for the first time. It provides the ability to compare dendrograms based upon two sets of traditional medicines. This research has also shown the importance of quantitative ethnobotanical techniques in the interpretation of the resulting interviews, since this aspect of the study added new understandings to the different datasets. Moreover, this study confirmed that TM is generally homogenous among Cree Nations in Canada and in Québec. Communities were found to use the same plant species, and in similar ways. However, since both the Cree communities studied

reflect variation along geographical and floristic gradients, Elders and Healers have been shown to select different plant species depending on their availability in the local environment. In addition to this, it was shown that the Cree residing in Whapmagoostui preserved more TM and named medicines differently.

In addition to the above ethnobotanical study, *in vitro* experiments were carried out on medicinal plants in order to screen for antioxidant activity and allow for further comparisons. Although TM has been mentioned for its antidiabetic proprieties (Marles and Farnsworth 1995), including species used in Canada (McCune and Johns 2002), this work primarily measured antioxidant activity on medicinal plants used by the Cree in Québec. The research demonstrated the abundance of antioxidants in TM found within this province. Medicinal plants used in Whapmagoostui had especially high antioxidant capacity most likely due to the northern environmental pressures on plants (Savile 1972; Dalton 1995). Samples taken, particularly for *Larix laricina,* have shown comparable activity to ascorbic acid (vitamin C), Trolox® (vitamin E analog) as well as known flavonoids such as quercetin, catechin and epicatechin. Cree Elders and Healers have selected plants species with favourable antioxidants, such as vitamins C and E, which could play a role in controlling oxidative status in diabetics, as Douillet *et al.* (1998) have shown.

Both the ethnobotanical study and the analysis of antioxidants have underlined that Pinaceae and Ericaceae are important TM medicine and should be prioritized for consumption. These families are commonly used by Elders and Healers; they treat many T2D symptoms and show antioxidant abundance related in part to their phenolic content. *Kalmia angustifolia, Larix laricina* and *Picea* spp. are widespread species in the boreal forest (Richardson 1998), even though Whapmagoostui is also geographically part of the hemiarctic area (Scott 1995). Although some studies have demonstrated correlations between bioassay results with phenolic content on edible plant products (Katsube *et al.* 2004) or on medicinal plants (Cai *et al.* 2004), this research has also shown such correlations between scientific and traditional knowledge. In other words, it has established positive correlations between results found from ethnobotanical data,

antioxidants and phenolic content. Therefore, Elders and Healers have selected effective medicinal plants rich in antioxidant properties that are based on phenolics. Since consumption of antioxidants is beneficial for T2D patients (Farvid *et al.* 2005), Cree medicine could prove to be an invaluable method for treating T2D symptoms.

8.1. Limitations

During the course of the ethnobotanical and experimental projects, it was recognized some aspects could be optimized in future studies. In the first part of this project, most interviews with participants were based on one meeting, whereas more interview sessions would have potentially created a higher level of trust and confidence (Lipp 1989) among participants and potentially provided more information on plant uses and knowledge. Ideally the Cree name and its syllabic should have been written by the Elder or the Healer instead of the interpreter during the interview. In the present study only one Elder provided such information. Although fresh plant material was shown in each interview to the participant to confirm the Cree name, during the fieldwork more visits in the bush with the Elders and Healers would have validated plant identification more accurately due to the environmental information (Cunningham 2001). Finally, as suggested by Oubré *et al.* (1997) a brief description of case history consistent with the diagnosis of T2D and photographs of diabetic symptoms could lead to more accuracy in determining plant and TM usage, as well as facilitate communication using a common language about the disease. However, this approach was not used in the questionnaire of the present ethnobotanical research.

In the second study, fresh material was only extracted using EtOH, whereas other extractions could give different results or might have captured additional compounds. For example, Owen and Johns (2002) have measured medicinal plant extracts with different organic solvents (hexane, chloroform, ethylacetate and water), while Cowan (1999) has based his study on different extraction methods to determine different isolated molecules. In water extraction, saponins and anthocyanins would be isolated, but not well extracted, in the ethanolic extraction process.

However, in the present study, there were logistical limitations in running different extraction methods. Since many samples were analysed, which also included non-medicinal plant samples, it could be more effective to reduce the sample numbers in order to conduct bioassays sooner in the process. Indeed, time plays a role in the degradation of molecules. For example, volatile oils could possibly be inactive in *Juniperus communis, Abies balsamea* (Leung and Foster 1996), *Myrica gale* (Stuart 1998) *Vaccinum vitis-idaea* (Marles *et al.* 2000) and *Betula glandulosa* (Degroot *et al.* 1997) after a certain period of time.

Although DPPH, TBARS and CD were used, each presented particular weaknesses. DPPH assay cannot detect intermediates during the oxidation process (Ursini *et al.* 1994). Although widely used, TBARS is not specific and TBA reacts with a number of components present in biological samples although it was combined with CD for lipid peroxidation as suggested by Devasagayam *et al.* (2003).

8.2. Future research

Since a multidisciplinary team was created in 2003, the initial ethnobotanical investigation collected at Mistissini has inspired several studies (Leduc *et al.* 2006; Spoor *et al.* 2006; Grandi 2006). The extension of the study in Whapmagoostui contributed to advancing the knowledge of traditional healing in northern Québec. Since there are nine Cree of Eeyou Istchee communities in the north of Québec (East Cree Language 2005), with different dialects (Cree Cultural Institute 2005) and living in different ecoclimatic regions (Scott 1995), these different communities could and should be approached in order to obtain additional information concerning TM usage. It would also be valuable to facilitate comparative studies with other Nations living in the boreal forest, which could involve other First Nations communities, including Algonquins, Attikameks and Innus, for example. Furthermore, a study could be conducted within the same area as Kuujjuaraapik-Whapmagoostui in order to evaluate other potential medicinal antidiabetic species. Moerman (1996) has made such comparisons among many First Nations groups. In such an effort, the integration and equal collaboration with these communities, especially the participation of Elders and Healers, would be essential.

Despite its valuable properties, the younger generation of Cree do not use TM (Elders and Healers, *pers. comm.*). Moreover, as with other indigenous populations, the youth are exposed to environmental stresses such as poor diet, lack of physical activity and obesity, which are in part responsible for the T2D problem among the Cree (Young *et al.* 2000; CBHSS 2001). Following the validation of TM for the treatment of T2D through the collaboration of Elders and Healers with scientific investigators, it would prove invaluable to involve participants in the community in order to promote its use among youth for disease prevention.

In relation to this objective, Grandi (2006) has questioned members of the community in Mistissini using a dietary survey and by doing a nutritional assessment of the village. The lower T2D rate in Whapmagoostui (Brassard 1991; CBHSS 2001) could be due to the geographical isolation, the superior and more consistent use of TM and/or the different diet that is probably based on traditional food. Indeed, Adelson (1992) showed that the people of Whapmagoostui still practiced traditional activities (hunting and berry picking), which results in eating traditional food and therefore healthier food. This last point could be verified with a nutrition questionnaire administered among the community of Whapmagoostui and then compared to the results from the survey completed in Mistissini. Based on these results, further research in clinical endocrinology and health services among the population could be initiated.

Since there are a multitude of tests in numerical taxonomy (Legendre and Legendre 1998; Podani 2000), and since quantitative ethnobotany in this study has shown the importance of each medicinal species between communities, it would be interesting to perform a correspondence analysis as done by Leduc *et al.* (2006). This technique isolates those plant species within a large ethnobotanical data set which are most used for a specific symptom. For example, *Juniperus communis* has been found mostly in the treatment of urinary problems, while *Vaccinium vitis-idaea* is almost always used to treat blurred vision specifically. This could definitely be validated in further studies by correspondence analysis.

As a follow up to the preliminary antioxidant measurements of medicinal plants carried out in this investigation, other studies could be initiated. Lipid peroxidation of LDL plays a role in artherosclerosis, which has relevance because it is known that diabetics are at high risk of developing cardiovascular disease (Baynes and Thorpe 2000; Levy *et al.* 2000). Since, eight prioritized plants have demonstrated antioxidant activity during *in vitro* experiments on LDL molecules subjected to oxidation (*Juniperus communis, Kalmia angustifolia, Larix laricina, Picea glauca, P. mariana, Rhododendron groenlandicum, R. tomentosum* and *Vaccinium vitis-idaea*), further projects might determine the antioxidant effects of these plants in *in vivo* diabetic models in order to guide possible clinical research. *Larix laricina* has shown the highest antioxidant capacity among all bioassays tested, and would therefore be the best candidate for further analysis. As a species commonly used as traditional food and TM (Moerman 1996 and 1998), it is far less known for its pharmacological value and would therefore make an excellent candidate for this type of research (Glasby 1991; Powell and Raffa 1999a, b). Additional information could validate the antidiabetic effect of this TM among Cree of Eeyou Istchee.

A primary pharmacological study on the medicinal plants of Mistissini was realized by Spoor *et al.* (2006). They studied the antidiabetic effects of the most promising species using *in vivo* animal models. *Sarracenia purpurea, Rhododendron groenlandicum* showed significant insulinomimetic activity and *Picea mariana* appears to contain an insulin-sensitizer. A similar experiment could be realized on the above medicinal plants in future research.

The consumption of antioxidant vitamins such as vitamins C and E (Rifici and Khachadurian 1993), flavonoids and other phenolic compounds may prevent the formation of ROS and contribute to the inhibition of LDL oxidation (Rice-Evans 1995) Since the indigenous people of Canada are more predisposed to develop vitamins A and C deficiencies (Berkes and Farkas 1978; Hoffer *et al.* 1981), and since the TM of the Cree of Eeyou Istchee TM has shown impressive antioxidant activity, supplementation programs using TMs could prove to be a promising complementary tool in treating T2D

symptoms (Young *et al.* 1992; Sinclair *et al.* 1992; Gokkusu *et al.* 2001; Skeaff 2002). Incorporation of these plant sources in the diet could also help to reduce the existing vitamin deficiencies, therefore contributing to T2D prevention (Hoffman *et al.* 1967; Turner 1995; Cunningham 1998).

Corresponding to knowledge of the vast list of phenolic compounds (Buchanan *et al.* 2000) that occur in high amounts in many plants (Proteggente *et al.* 2003), phenolic content of twenty-four medicinal plants used by the Cree of Eeyou Istchee has been documented. Additional efforts in future studies could focus on the isolation and description of active molecules among the plant species with HPLC and other techniques, such as those demonstrated by Lee *et al.* (2004). Additional antioxidant assays that could be valuable include 2,2'-diazobis(2-amidinopropane) dihydrochloride (AAPH) (Biffanti *et al.* 1994), nitroblue tetrazolium (NBT)/xanthine oxidase (McCune and Johns 2002), total reactive antioxidant potential (TRAP), oxygen radical absorbance capacity (ORAC), Trolox® equivalence antioxidant capacity (TEAC) and ferric ion reducing antioxidant power (FRAP) (Llesuy *et al.* 2001; Huang *et al.* 2005). Devasagayam *et al.* (2003) have proposed expensive modern techniques more specific to lipid peroxidation measurement such as HPLC, spectrofluorometry, mass spectrometry and chemiluminescence.

The present research study has attempted to expand knowledge of TM used by the Cree of Eeyou Istchee, screened TM with high antioxidant abundance and validated traditional information with scientific experimentation and laboratory analysis. Further steps could help determine the antidiabetic effect of using TM with the above proposed studies in order to prevent T2D among the Cree Nation.

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Appendices

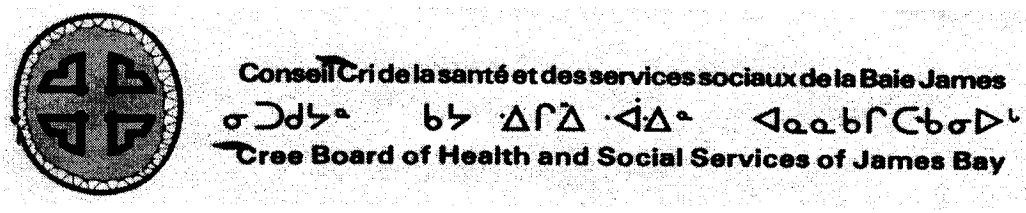
Appendix 1.

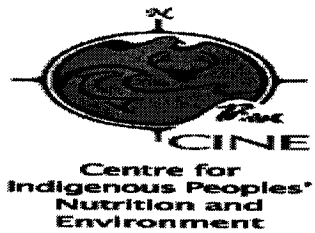
Coastal and continental vegetation around Whapmagoostui and Mistissini

	Whapmagoostui		Mistissini	Author (s)
Ecoclimatic region	Mid-subarctic		Mid-Boreal	Scott (1995)
	Low-subarctic and Mid-subarctic		Humid mid-boreal	CCELC (1989)
	Hemiarctic; forest tundra		---	Deshaye and Cayouette (1988)
	Hemiarctic		---	Deshaye and Morisset (1985)
	Hemiarctic		---	Payette and Lepage (1977)
	Hemiarctic (55.5°)		Subarctic (51° until 55.3°)	Malaurie and Rousseau (1964)
Productivity	125 g/m^2/yr		800 g/m^2/yr	Berkes and Farkas (1978)
Wetland	Low subarctic (51-75 %)		---	Scott (1995)
Vegetation formation or bioclimatic zone	Boreal,Tundra ecotone		Boreal-taiga	Scott (1995)
	Coastal	*Continental*		
	Southern forest tundra	Boreal forest (Open lichen woodland)	---	Department of Mines and Technical Surveys (1974); Scott (1995)
	Boreal (High Subarctic)	Hemiarctic	---	Hydro-Québec (1993a)
	Hemiarctic with lichen heath	High-subarctic with wooded heath		Ducruc (1976)
	Maritime with Lichen heath, *P.glauca*	Continental *P. mariana*	---	Payette (1975); Payette and Filion (1975); Payette and Lepage (1977)
Number of species	Subarctic forest : 488		453	Deshaye and Morisset (1985)
	Mid-subarctic and Richmond Golf: 400		414	Forest and Legault (1977); Payette and Lepage (1977)
	Manitounuk island: 325		---	Deshaye and Cayouette (1988)
	Whapmagoostui: 530		---	Hydro-Québec (1993a)
	Eau-Claire Lake: 250		---	Deshaye and Morisset (1985)
	---		453	Blondeau (2003)

Appendix 2.

The consent letter, from ethical approach and approval by the ethical committee





Consent letter of participation

Research study to identify medicinal plants that can help Cree people with the symptoms of diabetes

Professors Timothy Johns, McGill University, Alain Cuerrier, Jardin botanique de Montréal (Université de Montréal) and Marie-Hélène Fraser, a master's student of McGill University, will work with Cree Elders and Healers on a research study. The reason for doing the research study is to identify which medicinal plants might be able to help Cree people with the symptoms of diabetes. A general goal is to evaluate the plants and provide the information back to the community, so that traditional medicines can be best used by the local clinic.

Marie-Hélène Fraser will work with the Elders and Healers to identify and pick the plants. Each plant will be put onto a card, named and covered in plastic. These cards will be kept at the Cree Cultural Institute, community schools in Eeyou Istchee and at the Jardin Botanique de Montréal.

When the plants are being picked, the researchers Professors Johns and Cuerrier will respect sacred places. They will also follow instructions from the Cree Elders and Healers about the proper way to respect and pick the plants.

Ms. Fraser will ask each Elder and Healer if he or she agrees to be recorded and have his or her picture taken. She will explain the reasons to the participant. The name of each Cree Elder and Healer will be kept confidential unless the person says his or her name can be used. Moreover, all personal information about participants related to the study will be kept confidential. Moreover, the information of participants, useful for the study, such as antidiabetic plants species and their medicinal used, will not be associated with a specific Elders or Healers, but will be resuming in general with other information from other participant.

Each Elder and Healer will decide what information she or he wants to share with the researchers. She of he will decide which questions to answer. She of he may withdraw from the study at any time.

The Cree Board of Health will sign an agreement with each of the research organizations involved in this project. This agreement will set up rules about how Professor Johns and the other people working with him will write about what the Elders and Healers have shared before information is published.

Jane Blacksmith and Bella Petawabano are members of the 'Research Committee' of the Cree Board of Health, and they will see what Professor Johns and the other people working with him have written and will make comments on it.

The researchers also acknowledge the Elders' and Healers' concern that, during interviews, incomplete information or miscommunication could occur and lead to inappropriate use of the knowledge shared by the Elders and Healers. While the researchers take full responsibility, if anything goes wrong, they will make sure that all information provided by the Elders and Healers is used properly.

Professor Cuerrier will keep Jane Blacksmith, Lily Sutherland, Dianne Reid and Solomon Awashish up-to-date about what is happening. Professors Johns and Cuerrier and student Fraser will keep the Elders and Healers informed about the research study, along with other community members.

I agree to participate to the antidiabetic plants project with conditions described above.

Name of Cree Elder,Healer	**(Signature of Cree Elder,Healer)**	Date
Researcher	**(Signature of researcher)**	Date
Interpreter	**(Signature of interpreter)**	Date

My picture can be taken during the course of the research ☐
(do **not** tick the box is you do not wish your picture to be taken)

My name may be used in communicating information about the research ☐
(do **not** tick the box if you wish your name to be kept confidential)

Appendix 3.

Questionnaire

Name of Elder or Healer : *On another secret page, to keep the privacy.*
Age : _____
Birth place : _____
How would you define health : _____
And illness, disease : _____
What is your conception or understanding of diabetes : _____
Causes : _____
Is there a relationship between traditional food/diet and diabetes : _____
Diabetes Yes, No: _____

Place of interview : _____
No (Recording): _____
Length of interview : _____
Date of interview : _____
Symptom : _____ Date _____
Other symptoms : _____
Cree plant name : _____
Latin name : _____
Etymology : _____
Plant/animal part used : _____
Plant abundance : _____
Plant habitat : _____
Plant is seen as medicinal material or food _____
Preparation : _____
Plant toxicity : _____
Side effects : _____
Plant posology (amount,frequency,time of intake) : _____
Collecting date/season : _____ Time of day : _____
Collecting ritual : _____
Cree Names related to plant parts : stem _____ branch _____
bark _____
root _____
leaf _____
bud _____
flower _____
fruit _____
Classification : 1 name to cover all plant life _____
Fungi _____
Lichens _____
Ferns _____
Trees _____
Shrubs _____
Herbs _____
Plant-animal interactions : _____
Myth, legend, story : _____
Who did you learn these information from? : _____

Appendix 4.

54 species collected at Whapmagoostui and their Cree name

Achillea borealis Bong.	Miskogotuck, Mishishstock, Wabish
Arctostaphylos alpina (L.) Spreng.	Adkoominatoock
Armeria maritima (P. Mill.) Willd. subsp. *sibirica* (Turcz. ex Boiss.) O. Hyl.	Sheesheeminshounn
Artemisia campestris L. subsp. *borealis* (Pall.) Hall & Clements	Nesjeegun
Bartsia alpina L.	Miniskshoue
Betula grandulosa Michx.	Skinmeeshougontick, Itigoobikwisk
Botrychium lunaria (L.) Sw.	Weesheejackush
Campanula rodundifolia L.	Anstinnigansh
Castilleja septentrionalis Lindl.	Nibish
Chamerion angustifolium (L.) Holub	Michskishoe, Nischiikhan
Chamerion latifolium (L.) Holub	Neebeshe
Cornus canadensis L.	Wibish
Dendranthema arcticum (L.) Tzvelev subsp. *polare* (Hultén) Heywood	Anmoustoonn
Diapensia lapponica L.	Mistanmeeshonn, Nabebish
Diphasiastrum alpinum (L.) Holub	Bastchgowgan, bashenagawgun
Diphasiastrum complanatum (L.) Holub	Bastchgowgan, Bashenagawgun
Equisetum arvense L.	Neeskann, Miskouchoe
Eriophorum scheuchzeri Hoppe	Neeskann, Miskouchoe
Euphrasia frigida Pugsley	Nibish
Fucus spp.	Shashabee
Hippuris vulgaris L.	Astchebaog
Honckenya peploides (L.) Ehrh.	Weneboug
Huperzia selago (L.) Bernhard	Bachinakouakan, Pusnakongansk
Kalmia polifolia Wang.	No name
Lathyrus japonicus Willd.	Shabagooshoom, Misuskiwcho, Nabish
Linnaea borealis L.	Nibish, Mestug wou meens
Loiseleuria procumbens (L.) Desv.	Itchkaseeboaukish
Minuartia stricta (Sw.) Hiern	Nibish, Cakouboush
Moneses uniflora (L.) A. Gray	Nibish
Myrica gale L.	Estiminatuck
Orthilia secunda (L.) House	Nibish
Parnassia palustris L. subsp. *neogaea* (Fern.) Hult.	Nibish
Pedicularis labradorica Wirsing	Neebeshe
Pinguicula vulgaris L.	Nibish
Plathantera dilatata (Pursh) Lindl. ex Beck	Neebeshe
Potentilla crantzii (Crantz.) Beck	Nibish
Pyrola grandiflora Radius	Minnishetuck, Nibish, Wesjedashu

Appendix 4. *Continued*

Rhytidium rugosum (Hedw.) Kindb.	Beastaskugg, Beastaskumuk
Rubus chamaemorus L.	Shicoudaw
Salix arctophila Cock. ex Heller	Waskayabaduk, Washayabaduk, Nibshee
Salix uva-ursi Pursh	Eeyoudackoonn , Miwishuck, Nibi
Saxifraga aizoides L.	Nibish
Saxifraga paniculata P.Mill.	Nabshishe
Saxifraga tricuspidata Rottb.	Miniksho , Wichichimin
Sibbaldiopsis tridentata (Ait.) Rydb.	Wartabee or wachichistatuk , nibish
Sphagnum capillifolium (Ehrh.) Hedw.	Awasistche , Awashesstees, Washichistchee
Sphagnum russowii Warnst.	Awasistche, Awashesstees, Misheskosha, Mistoushann
Solidago multiradiata Ait.	Amousyoonn , Misuskiwcho , Nabish
Stellaria longipes Goldie	Mickshi
Stereocaulon spp.	Wapskimok
Tanacetum bipinnatum (L.) Schultz-Bip. subsp. *huronense* (Nutt.) Breitung	Neebeshe, Miskishaw
Tofieldia pusilla (Michaux) Persoon	Nibish
Trientalis borealis Raf.	Secgoodaa , Nibish
Umbilicaria muhlenbergii (Ach.) Tuck.	Whakoonch pl., Whakoon 1, Waganj

Appendix 5.
Known secondary metabolites for plants studied.

Antioxidant	Secondary metabolites	Plants [a]	Authors
Vitamins	β-carotene:Vitamin A [b]	Cr; En; Gh; P.sp; Spp; Vu; Vvi *Ca; Ea; Sa; Rc*	Glasby 1991; Czeczuga 1994; Hoffman *et al.* 1967
	Ascorbic acid:Vitamin C [b]	Ab; En; Gh; Jc; Lm; Pg; Pm; Pb; Rg; Spp; Vu; Vvi; *Ea; Sa; Rc Ca; Ea;*	Arnason *et al.* 1981; Kuhnlein and Turner 1991; Nagai *et al.* 2005; Leung and Foster 1996; Hoffman *et al.* 1967; Fediuk *et al.* 2002; Mccoll 2002
Terpenoid and essential oil	Volatile oil	*Mg*	Mathiesen *et al.* 1995-1996a,b-1997; Stuart 1998
	Terpene	Jc; Rg; Sd;	Leung and Foster 1996; Barjaktarovic *et al.* 2005; Angioni *et al.* 2003; Marles 2001
	Terpenoids	Ab; Air; Cr; En; Jc; Ka; Ll; Pm	Glasby 1991; Fediuk *et al.* 2002; Burke *et al.* 1989;
		Pb; Rg; *Ab; Bg; Mg; Thb; Rc*	Powell and Raffa 1999a-b; Skene *et al.* 2000; Leung and Foster 1996; Marles 2001
Phenolic and Polyphenolic [b]	General	En; Pm; Pb; Pg; Psp; Spp; Sd; Vu;	Krasnov *et al.* 2000; Arriagaginer *et al.* 1993;
		Vvi *Ca; Bg; Ea; Sr; Rc*	Kahkonen *et al.*1999; Katsube *et al.* 2003; Zulaica-Villogomez *et al.* 2005; Pinelo *et al.* 2004; Han *et al.* 2003;
			Glasby 1991; Jacquemart 1996; Katsube *et al.* 2003; Kiss *et al.*2004; Rey *et al.* 2005; El-Ansari *et al.*2002; Oh *et al.*2004; Amarowicz *et al.* 2004; Rasmussen *et al.* 1995; Leung and Foster 1996; Marles 2001

Appendix 5.
Continued

Antioxidant	Secondary metabolites	Plants [a]	Authors
	Flavonoids [b]: Quercetin, Catechin, Anthocyanins	En; Jc; Ka; Ll; Pg; Pm; Spp; Sd; Vu; Vvi; *Ab; Aml; Bg; Cr;Ca; Ea; Mg; Sa; Rc;*	Fediuk *et al.* 2002; Leung and Foster 1996; Berg 2003; Glasby 1991; Marles *et al.* 2000; Smolarz *et al.* 2000; Katsube *et al.* 2003; Lauranson *et al.* 1995; Kiss *et al.* 2004; El-Ansari *et al.* 2002; Oh *et al.* 2004; Hakkinen *et al.* 1999; Malterud *et al.* 1996; Small and Catling 1999; Mallik 2003
	Flavones: Quercetin	En; Sp; Vvi; *Ab; Hv;*	Fediuk *et al.* 2002; Romeo *et al.* 1977; Smolarz *et al.* 2000; Zheng and Wang 2003; Glasby 1991; Pascal-Lorber *et al.* 2004
	Tannins [b]	Ka; Sd; Vvi; *Ca;* Vu	Arnason *et al.* 1981; Marles *et al.* 2000; Marles 2001 Ho *et al.* 2001; PDR for Herbal Medicine 1998
	Salicins	Spp;	Chrubasikyr *et al.* 2000
	Flavonols	Sp; Vu; *Ca; Lp;*	Sheridan and Griesbach 2001
			Glasby 1991; Jacquemart 1996; PDR for Herbal Medicine 1998; Cuendet *et al.* 2000
	Coumarin [b]	En; Vu; Vvi; *Ab;*	Fediuk *et al.* 2002; Glasby 1991
Alkaloids	General	En; Vu; *Ab; Cr; Hv;*	Fediuk *et al.* 2002; Glasby 1991; Degroot *et al.* 1997; Damtoft et ak 1994
	Toxic	Ka; Vu; Vvi	Glasby 1991; Burke *et al.* 1989; Mancini and Edwards 1979; Marles *et al.* 2000

[a] Medicinal plant and *non-medicinal plants* are listed by their first letter of genus and species. Abbreviations are listed Table 1 (Manuscript 2).
[b] Hypoglycaemic agents (Marles and Farnsworth 1995)