Canadian ginseng (*Panax quinquefolius*): A pharmacological review

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ABSTRACT

Panax quinquefolius has been used for centuries by native Amerindians and in Traditional Chinese medicine, due to its several beneficial and healing properties. In traditional medicine, it is considered to be complementary with the *Chinese ginseng, P. ginseng: P. quinquefolius* is a yang tonic, that has cooling effect and promotes respiratory and digestive health; whereas *P. ginseng* is a yin tonic that has a warming effect, and promotes a healthy circulatory system. These activities are reported to be coming from a group of actives molecules specific to the Panax genus, some triterpenoid saponins called ginsenosides. Many studies reported the pharmacological activities of *P. quinquefolius* and its ginsenosides, including anti-diabetic, anti-cancer, anti-fatigue, anti-inflammatory, antioxidant, cardio-protective and immunomodulatory properties.

KEYWORDS:

Canadian ginseng, ginsenosides, *Panax quinquefolius,* saponins

I. INTRODUCTION

Ginseng (*Panax* spp.) is a slow-growing perennial plant from Order Apiales and Family Araliaceae (Kochan and Chmiel, 2013). For thousands of years, this group of plant has been valued for their medicinal properties, especially in Asia where it is considered as a panacea (Cruse-Sanders and Hamrick, 2004). The name *Panax* comes from the Greek: "pan" = "all" and "axos" = medicine", meaning the cure-all plant (Yun, 2001). Among the *Panax*, three species are particularly known as medicinal plants in East Asia and in North America: *Panax ginseng*, *Panax notoginseng* and *Panax quinquefolius* (Wang et al., 2016). The last one, also called Canadian ginseng, is less known in European countries despite its interesting properties (Punja, 2011), which complements the ones of the well-known Chinese ginseng, *P. ginseng* (Chen et al., 2008). *P. quinquefolius* L. is also known as *Aralia quinquefolia* L. (Flora of China, 2018), Canadian or American ginseng, or five fingers (Sinclair, 2008). It was employed for centuries by native Amerindians as a traditional medicinal herb before it was "re-discovered" by Europeans in the 18th century and exported to China, which gave rise to a lucrative market (Fauchon, 2000).

P. quinquefolius herb takes generally 5 to 8 years to reach maturity. Mature plants are is 20 to 50 cm tall, with a short, main root and stem. The palmate leaves have long petiole and 3-4 oblong-obovate leaflets. The inflorescence is solitary, with a terminal umbel of 6 to 20 small green-white flowers (Fig. 1). The flowering period is from May to June, while the fruits, in the form of bright red drupes, appear from June to September (Liu et al., 2015; Persons and Davis, 2014; Sinclair, 2008).

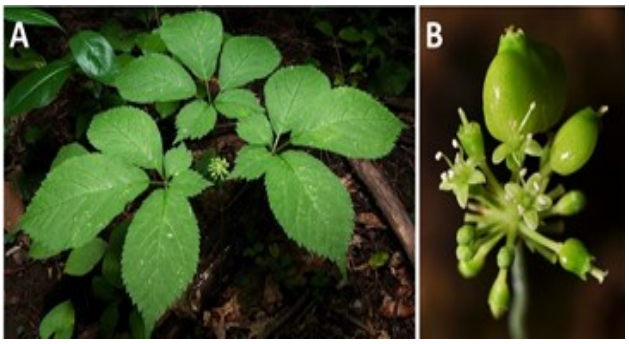

Figure 2: *P. quinquefolius* leaves (A), flowers and seeds (B) – Photographer: David Smith.

It is native to Canada and the United States. It is currently distributed through the temperate forest areas from Southern Quebec to Minnesota and South Dakota, in the North of Oklahoma, the Orzac Plateau and Georgia (Court, 2000), where it grows in well-drained, humus-rich soils (Bennett et al., 2011). Because of intensive harvest, *P. quinquefolius* is now considered as a threatened species. It was designated as Endangered by the Committee for the Status of Endangered Wildlife in Canada (COSEWIC) in 2000 and has been listed with the same status under Schedule 1 of the Species at Risk Act (SARA) since 2003 (Environment Canada, 2015). It is also listed in the appendices II of the Convention on International Trade in Endangered Species (CITES, 2017). The distribution map of *P. quinquefolius* in North America, with conservation status, is presented in Fig. 2.

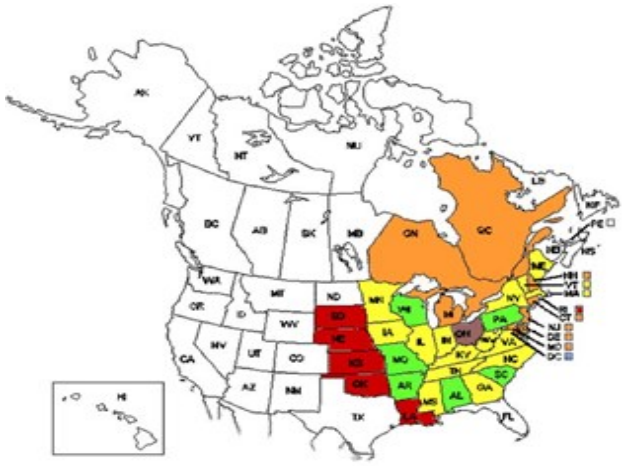

Figure 1: *Distribution of P. quinquefolius in North America. Conservation status: green – apparently secure; yellow – vulnerable; orange – imperiled; red – critically imperiled*

II. PHYTOCONSTITUENTS

P. quinquefolius phytoconstituents include saponins, essential oils, polysaccharides, peptides, polyacetylenic alcohols and fatty acids (Liu et al., 2015). The most significant group of active molecules is a group of triterpenoid saponins called ginsenosides. They can be classified into two groups according to the skeleton of their aglycone, namely dammarane- and oleanane-type (Biswas et al., 2017). Ginsenosides of dammarane-type are derivatives of three groups of molecule: protopanaxadiol (PPD-type, such as Rb1, Rb2, Rc and Rd), protopanaxatriol (PPT-type, such as Rg1, Re and Rf) or ocotillol such as Ro (Hwang et al., 2014; Kim et al., 2015).

More than 60 ginsenosides have been isolated from the roots, leaves, stems, flower buds and berries of *P. quinquefolius*, ginsenosides Rb1, Re, Rd, Rc, Rg1 and Rb3 being the major ginsenosides (Liu et al., 2015). In the root, which is the organ used for medicinal purposes, these main ginsenosides were identified through histochemical studies in periderm, cortex and xylem tissues (Ludwiczuk et al., 2006). The ginsenoside content is a parameter that could be used to distinguish *P. quinquefolius* and *P. ginseng*: the ginsenoside Rf is only found in *P. ginseng* whereas the pseudoginsenoside F11 is only found in *P. quinquefolius* (Koh et al., 2016). In addition, *P. quinquefolius* has a low ratio Rg1/Rb1 of less than 0.4, whereas *P. ginseng* has a higher Rg1/Rb1 ratio (Qi et al., 2011; Xiao et al., 2015).

Ginsenosides are biosynthetized via the mevalonic acid (MVA) pathway and the methylerythritol phosphate (MEP) pathway (Fig. 3). Ginsenosides are triterpenes, meaning terpenoids with 30 carbon atoms that arise from the union of dimethylallyl diphosphate (DMAPP) and two isopentyl diphosphate (IPP) molecules to form farnesyl diphosphate (FPP), synthetized by the farnesyl diphosphate synthase (FPS) (Gallego et al., 2014). Squalene synthase (SQS) is a single microsomal polypeptide enzyme that controls the dimerization of two FPP units to obtain the intermediate compound, squalene (Kim et al., 2015). Squalene is then converted to 2,3-oxidosqualene, the common intermediate in the biosynthesis of steroids and triterpenoids, by the action of the microsomal squalene epoxidase (SE) in the presence of O_2 and NADPH (Ding et al., 2015; Mugford and Osbourn, 2012).

The cyclization of 2,3-oxidosqualene via the 2,3-oxidosqualene cyclases (OSCs) is the branching point in the biosynthesis of sterols and triterpenoid saponins (Zheng et al., 2015).This step starts with the breaking of the oxirane ring in acid media, and after different rearrangements, two conformations are obtained: chair-boat-chair-boat (protosteryl cation, precursor of sterols) or chair-chair-chair-boat (dammarenyl cation, precursor of triterpenes) (Yendo et al., 2014). Dammarenediol synthase (DDS) reacts on the transient dammarenyl cation with water generating epimeric C-20 dammarenediol, precursor of the dammarene-type ginsenosides, whereas the oleanane-type ginsenosides derived from β-amyrin, catalyzed by β-amyrin synthase (β-AS) after the dammarenyl cation is converted into several cationic intermediates (Dokarry, 2010; Tansakul et al., 2006). The ginsenoside biosynthesis is then mainly achieved through two reaction steps: hydroxylation by cytochrome p450 (CYP) and glycosylation by uridine diphosphate (UDP)-dependent glycosyltransferase (UGT) (Yendo et al., 2014). In contrast to the limited gene number and common substrate of OSC genes within plants, UGTs and CYPs belong to large gene families with significant functional diversity diversity (Kim et al., 2015). Three CYP genes are involved in the biosynthesis of ginsenosides. The PPD is synthetized via the reaction of the CYP716A47 (protopanaxadiol synthase), which hydroxylate the dammarenediol-II at the C-12 position (Park et al., 2016); the PPT is synthetized via the reaction of the CYP716A53 (protopanaxatriol synthase), also called protopanaxadiol 6-hydroxylase (Yendo et al., 2014); and the CYP716A52 (oleanolic acid synthase) oxidize the β-amirin into oleanic acid for the synthesis of oleanane-type saponins (Xu et al., 2017). Finally, UDP-UGT catalyzes the addition of monosaccharides to the triterpene aglycones (Kim et al., 2015). This step often increases the water solubility of the triterpenes, but also their stability, storability, bioactivity or bioavailability (Jung et al., 2014).

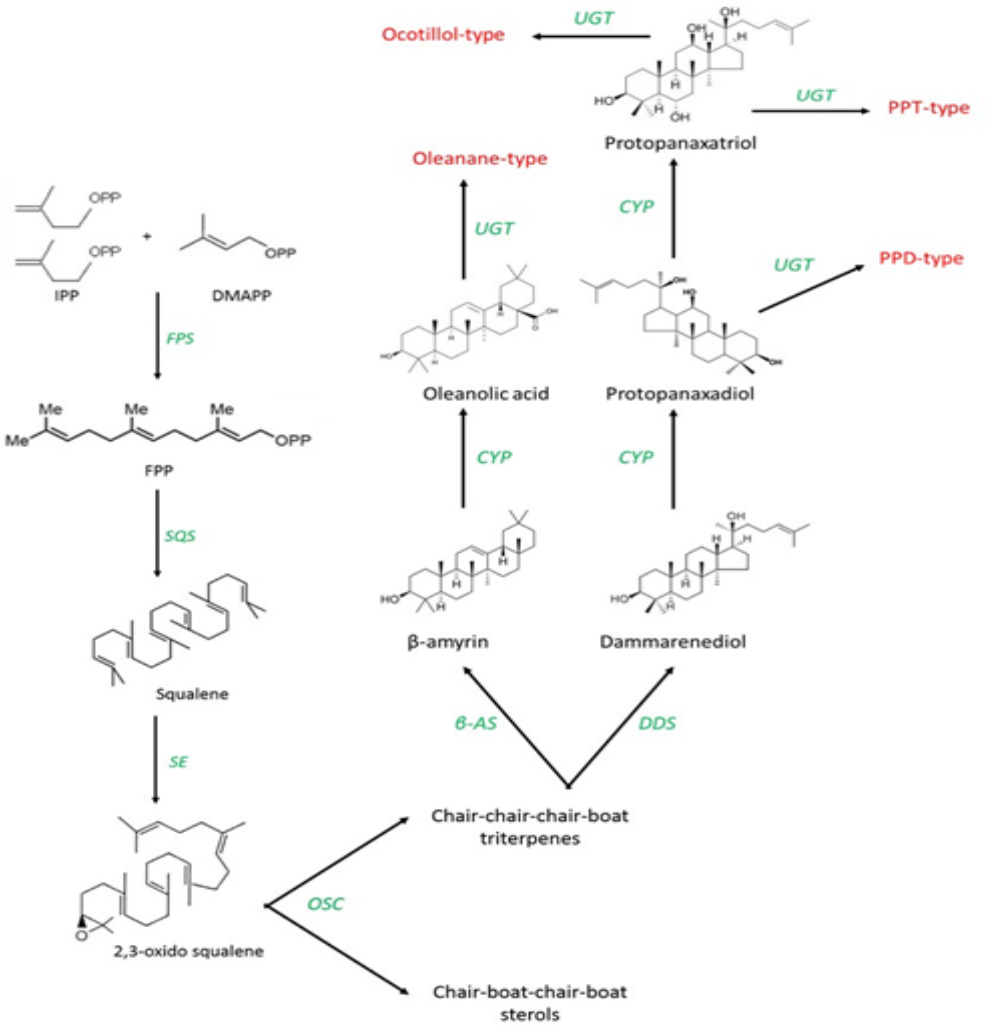

Figure 3: Biosynthesis pathway of ginsenosides.

III. TRADITIONAL USES

The The root of ginseng is used for medicinal purposes, generally to help relieve nervousness (Natural Health Product, 2015). The native Iroquois Indians used *P. quinquefolius* for various applications, such as analgesic, anticonvulsive, expectorant, digestive and general tonic (Bennett et al., 2011; Motsch, 2014). In Appalachia, it has traditionally been administered as a tea for general tonic purposes and as an aphrodisiac (Bennett et al., 2011).

In Asia, it began to be used after it was imported during the 1'700s (MDidea Brand, 2018). At that time, wild *P. ginseng* has already become rare; therefore the relative abundance and quality of wild P. quinquefolius opened the way for development of its cultivation as an export crop in the twentieth century (Hsu, 1979). It is now taken in China as a yang tonic, that has cooling effect and promotes respiratory and digestive health; whereas *P. ginseng* is considered as a yin tonic that has a warming effect, and promotes a healthy circulatory system (Club des Producteurs de Ginseng de la Vallée de la Gatineau, 2016). Consequently, *P. quinquefolius* is preferred by consumers in subtropical and tropical regions of Asia, as it is a cold or mild tonic, that will reduce "heat" in the system, while acting as a general tonic (MDidea Brand, 2018).

IV. PHARMACOLOGICAL ACTIVITIES

Many studies reviewed the pharmacological effects of *P. quinquefolius* and its active compounds, ginsenosides (Chen et al., 2008; Mancuso and Santangelo, 2017; Qi et al., 2010, 2011; Vogler et al., 1999; Wang and Yuan, 2008; Wu et al., 2007).

Anti-diabetic activity

P. quinquefolius has hypoglycemic immunomodulatory effects (Yarnell and Abascal, 2014). Both clinical and animal studies have indicated that its root has the ability to improve glycemic control (Ghorbani, 2013; Mucalo et al., 2012; Xie et al., 2005). Studies suggested that it possesses significant anti-hyperglycemic activity and may be beneficial to improve the management of type 2 diabetes (Xie et al., 2004a, 2004b).

The treatment with *P. quinquefolius* capsules reduced postprandial glycemia in nondiabetic subjects and subjects with type 2 diabetes (Vuksan et al., 2000). Alcoholic root extract of *P. quinquefolius*, administered daily at 200 mg/kg to diabetic mice for two to four months, has preventive effects on diabetic nephropathy through a combination of mechanisms including antihyperglycemic and antioxidant activities (Sen et al., 2012). In a randomized, placebo-controlled, crossover trial with thirty-nine type 2 diabetes-patients, the co-administration of Konjac-glucomannan-based fibre blend and *P. quinquefolius* (4.9-5.5 g/day and 2.7 g/day respectively) increased the effectiveness of conventional therapy through the reduction of HbA1c and lipid concentrations over 12 weeks (Jenkins et al., 2017). The addition of *P. quinquefolius* extract to conventional therapy in diabetes with concomitant hypertension also improved arterial stiffness and attenuated systolic blood pressure (Mucalo et al., 2013).

The safety of using *P. quinquefolius* supplementation on diabetic patients was demonstrated (Mucalo et al., 2014).

Anti-cancer properties

Aqueous extract of *P. quinquefolius* reduced the proliferation of breast cancer cells, with IC50 up to 100 mcg/ml, potentially linked to an anti-inflammatory mechanism. This might be applicable to the prevention of breast but also other cancers (Peralta et al., 2009). The aqueous-ethanolic extract of heat-processed *P. quinquefolius* root showed anti-proliferative activity on human breast cancer cells (Wang et al., 2008). Ginsenoside Gg3, also isolated from heat-processed *P. quinquefolius*, contributed to the apoptotic cell death on human gastric cancer cells (Park et al., 2014). It was reported that the berries of *P. quinquefolius* may also serve a complementary role with the chemotherapeutic agents in treating cancer, as the ethanolic extract seemed to enhance the tumoricidal activity of cisplatin against human breast carcinoma cells (Aung et al., 2006). Other studies demonstrated the anti-cancer activity of *P. quinquefolius* lipid-soluble extract such as hexane extract (Lee et al., 2009).

Ginsenoside Rb1, isolated from *P. quinquefolius* and *P. notoginseng*, exhibited potent cytotoxicity on cancer stem/tumor initiating cells, by suppressing its self-renewal without regrowth and sensitizing the cells to clinically relevant doses of cisplatin and paclitaxel. These effects were associated with inhibition of Wnt/β-catenin signaling and epithelial-to-mesenchymal transition (Deng et al., 2017). 20(S)-protopanaxadiol from both *P. quinquefolius* and *P. ginseng* inhibited the growth and induced cell cycle arrest in colon cancer cells *in vitro*. The investigation of several parameters suggested that this anticancer activity was mediated through targeting nuclear-factor κB, Jun N-terminal kinase and MAPK/ERK signaling pathways (Gao et al., 2013). The same conclusion was reached in other studies (Li et al., 2010a; Saw et al., 2010).

Anti-fatigue activity

The saponins and proteins isolated from *P. quinquefolius* had anti-athletic fatigue effects on mice treated with 100 mg/kg and subjected to swimming enduring exercises (Qi et al., 2014; Tang et al., 2009). An anti-fatigue effect was perceived by patients with cancer-related fatigue treated with 1'000 and 2'000 mg doses of *P. quinquefolius* daily (Barton et al., 2010).

Anti-inflammatory properties

A ginseng essence, comprising four medicinal herbs including *P. quinquefolius*, reduced inflammation and fibrosis in carbon tetrachloride-liver injury rats, by attenuating oxidative stress (Lu et al., 2017). An *in-vitro* assay demonstrated that *P. quinquefolius* had inflammomodulatory activity on adipocyte treated with crude aqueous extract or polysaccharide extract (Garbett et al., 2016; Wilson et al., 2013). Supplementation with aqueous extract of *P. . quinquefolius* reduced exercise-induced muscle damage and inflammation compared to non-treated control, in male rats fed with 300 mg of extract per kg daily for 14 days before a single downhill running (Estaki and Noble, 2015). The saponin extract also inhibited the endoplasmic reticulum stress-activated nuclear transcription factor pathway and associated inflammatory response in chondrocytes; and attenuated the knee joint cartilage degeneration in rats (Xie et al., 2018). It was demonstrated that the polysaccharides of *P. quinquefolius* may have therapeutic implications in treatment of inflammation and inflammatory-related diseases (Wang et al., 2015).

Antioxidant properties

P. quinquefolius extract showed strong DPPH radical scavenging activity up to a concentration of 1.6 mg/ml, and exhibited effective antioxidant activity in both lipid and aqueous media by chelating transition metal ions and scavenging of free radicals (Kitts et al., 2000). Its alkali-extractable polysaccharides exhibited significant antioxidant activity in a dose-dependent manner (Yu et al., 2014). *P. quinquefolius* extract also increased total antioxidant capacity and decreased reactive oxygen species in human peripheral blood lymphocytes after Cs irradiation, compared to non-treated control (Lee et al., 2008).

Cardioprotective effects

The crude extract of *P. quinquefolius* was used to treat rat cardiomyocyte cells exposed to angiotensin II or tumor necrosis factor alpha to induce oxidative stress. The treatment induced dramatic increases in Nrf2 protein expression, Nrf2 nuclear translocation, Nrf2 transcriptional activity, direct Nrf2 binding to its target gene promoters, and expression of a group of anti-oxidative genes driven by Nrf2 in the cardiomyocyte cells; and inhibited the induced free radical formation and H2O2-induced cell death in the cardiomyocyte cells. These results demonstrated that *P. quinquefolius* crude extract suppressed oxidative stress and oxidative stress-induced cell death in cardiomyocytes through activating the Nrf2 pathway (Li et al., 2010b). Other studies showed that *P. quinquefolius* cardioprotective activity may be partly mediated by its free radical scavenging properties (Shao et al., 2004) and by the regulation of nitric oxide synthase expression (Wu et al., 2011).

Effect on neurocognitive functions

An acute, randomised, double-blind, placebo-controlled, crossover study investigated the effect of a standardized *P. quinquefolius* extract (Cereboost™, 10.65% ginsenosides) on neurocognitive functions in humans. The working memory performance was significantly enhanced after the treatment with 100 mg of extract (Scholey et al., 2010). The mechanism of action involves the enhancement of acetylcholine level via choline acetyltransferase gene expression and

neuroprotection (Shin et al., 2016). Treatment with *P. quinquefolius* 100 and 200 mg/kg significantly improved the cognitive impairment in stressed mice by reducing pro-inflammatory cytokine, acetylcholinesterase and corticosterone levels; and attenuating oxidative-nitrergic stress (Kumar, 2017).

P. quinquefolius was reported as being a potential neuroprotective agent against Parkinson's diseases (González-Burgos et al., 2015).

Immunomodulatory effect

A protein isolated from *P. quinquefolius* root had good immunoregulatory effects on murine peritoneal macrophages (Qi et al., 2016). The aqueous and polysaccharide extracts also had immunomodulatory effects on rat alveolar macrophages – as determined by increased production of nitric oxide, tumor necrosis factor and interleukin (Azike et al., 2011; Lui et al., 2012), in mice (Rinwa and Kumar, 2014) and in adipocytes (Wilson et al., 2011).

V. CONCLUSION

Because it has been used for centuries in several traditional medicines, particularly Chinese medicine, and because of its complementarity with the well-known medicinal plant *P. ginseng*, *P. quinquefolius* has been intensively studied in the last decades. Its active molecules – as well as its pharmacological properties – have been well characterized. The efficacy of *P. quinquefolius* in many diseases has been proven, especially in the treatment of diabetic patients.

REFERENCES

[1]. **Kochan E, Chmiel A.** Callus of American ginseng (Panax quinquefolius) as a source of ginsenosides – medicinal secondary metabolites. Biol Lett. 2013 Jan 1;50(1):27–34.

[2]. **Cruse-Sanders JM, Hamrick JL.** Genetic diversity in harvested and protected populations of wild American ginseng, Panax quinquefolius L. (Araliaceae). Am J Bot. 2004 Apr 1;91(4):540–8.

[3]. **Yun TK.** Brief introduction of Panax ginseng CA Meyer. J Korean Med Sci. 2001;16(Suppl):S3.

[4]. **Wang T, Guo R, Zhou G, Zhou X, Kou Z, Sui F, et al.** Traditional uses, botany, phytochemistry, pharmacology and toxicology of Panax notoginseng (Burk.) F.H. Chen: a review. J Ethnopharmacol. 2016 Jul;188:234–58.

[5]. **Punja ZK**. American ginseng: research developments, opportunities, and challenges. J Ginseng Res. 2011 Sep 25;35(3):368–74.

[6]. **Chen C, Chiou W, Zhang J**. Comparison of the pharmacological effects of Panax ginseng and Panax quinquefolium. Acta Pharmacol Sin. 2008 Sep;29(9):1103–8.

[7]. **Flora of China.** Panax quinquefolius in Flora of China @ efloras.org [Internet]. Flora of China - Panax quinquefolius. 2018 [cited 2018 Feb 2]. Available from:http://www.efloras.org/florataxon.aspx ?flora_id=2&taxon_id=200015253

[8]. **Sinclair A.** Panax quiquefolius (American Ginseng) in Canada: a case study [Internet]. NDF Workshop Case Study; 2008 [cited 2016 Oct 5]. Available from: http://www.conabio.gob.mx/institucion/cooperacion_internacional/TallerNDF/Links-Documentos/WG-CS/WG2-Perennials/WG2-CS5%20Panax(Canada) /WG2-CS5.pdf

[9]. **Fauchon C. L**e ginseng dans l'érablière. MAPAQ Lac Etchemin; 2000.

[10]. **Liu Y, Wang Z, Zhang J.** Dietary Chinese herbs [Internet]. Vienna: Springer Vienna; 2015 [cited 2016 Oct 31]. Available from: http://link.springer.com/10.1007/978-3-211-99448-1

[11]. **Persons WS, Davis JM.** Growing and marketing ginseng, goldenseal and other woodland medicinals. 2014.

[12]. **Court WE.** Ginseng: the genus Panax [Internet]. Australia: Harwood Academic; 2000 [cited 2016 Dec 6]. Available from: http://www.crcnetbase.com/isbn /9789058230348

[13]. **Bennett K, Clare BMS, Zietz AN, Mizur D, Kluge L, Hernandez M.** Appalachian plant monographs: Panax quinquefolius L. Appalach Cent Ethnobot Stud [Internet]. 2011 [cited 2016 Oct 17]; Available from: http://www.frostburg.edu/fsu/assets/File/ACES/panax %20quinquefolius%20-%20final(1).pdf

[14]. **Environment Canada.** Recovery strategy for the American ginseng (Panax quinquefolius) in Canada [proposed]. Ottawa: Species at Risk Act Recovery Strategy Series. Environment Canada; 2015 p. 1–29. (Species at Risk Act Recovery Strategy Series).

[15]. **CITES. CITES** appendices I, II and III [Internet]. Concention on International Trade in Endangered Species of Wild Fauna and Flora; 2017 [cited 2017 Nov 16]. Available from: https://www.cites.org/eng/app/appendices.php

[16]. **Biswas T, Mathur AK, Mathur A.** A literature update elucidating production of Panax ginsenosides with a special focus on strategies enriching the anti-neoplastic minor ginsenosides in ginseng preparations. Appl Microbiol Biotechnol [Internet]. 2017 Apr 14 [cited 2017 Apr 24]; Available from: http://link.springer.com/10.1007/s00253-017-8279-4

[17]. **Hwang CR, Lee SH, Jang GY, Hwang IG, Kim HY, Woo KS, et al.** Changes in ginsenoside compositions and antioxidant activities of hydroponic-cultured ginseng roots and leaves with heating temperature. J Ginseng Res. 2014 Jul;38(3):180–6.

[18]. **Kim Y-J, Zhang D, Yang D-C.** Biosynthesis and biotechnological production of ginsenosides. Biotechnol Adv. 2015 Nov;33(6):717–35.

[19]. **Ludwiczuk A, Weryszko-Chmielewska E, Wolski T.** Localization of ginsenosides in Panax quinquefolium root tissues. Acta Agrobot. 2006;59(2):7–15.

[20]. **Koh HL, Wee HN, Tan CH.** Ginseng and ginseng products 101: what are you buying? New Jersey: World Scientific; 2016. 400 p.

[21]. **Qi L-W, Wang C-Z, Yuan C-S.** Ginsenosides from American ginseng: chemical and pharmacological diversity. Phytochemistry. 2011 Jun;72(8):689–99.

[22]. **Xiao D, Yue H, Xiu Y, Sun X, Wang Y, Liu S.** Accumulation characteristics and correlation analysis of five ginsenosides with different cultivation ages from different regions. J Ginseng Res. 2015 Oct;39(4):338–44.

[23]. **Gallego A, Ramirez-Estrada K, Vidal-Limon HR, Hidalgo D, Lalaleo L, Kayani WK, et al.** Biotechnological production of centellosides in cell cultures of Centella asiatica (L.) Urban. Eng Life Sci. 2014;14:633–42.

[24]. **Ding C, Zhao C-L, Chen Z-J, Wei F-G, Song D-G, Miao K-R.** Bioinformatics analysis of the squalene synthase gene and the amino acid sequence in ginseng species. Int J Clin Exp Med. 2015;8(8):12818.

[25]. **Mugford ST, Osbourn A.** Saponin synthesis and function. In: Bach TJ, Rohmer M, editors. Isoprenoid Synthesis in Plants and Microorganisms [Internet]. New York, NY: Springer New York; 2012 [cited 2018 Feb 5]. p. 405–24. Available from: http://link.springer.com/10.1007/978-1-4614-4063-5_28

[26]. **Zheng X, Luo X, Ye G, Chen Y, Ji X, Wen L, et al.** Characterisation of two oxidosqualene cyclases responsible for triterpenoid biosynthesis in Ilex asprella. Int J Mol Sci. 2015 Feb 5;16(12):3564–78.

[27]. **Yendo A, Costa F, Costa C, Colling L, Gosmann G, Fett-Neto A.** Biosynthesis of plant triterpenoid saponins: genes, enzymes and their regulation. Mini-Rev Org Chem. 2014 Sep 15;11(3):292–306.

[28]. **Dokarry M. β-amyrin synthase:** Investigating the structure and function of an oxidosqualene cyclase involved in disease resistance in oats [PhD Thesis]. University of East Anglia; 2010.

[29]. **Tansakul P, Shibuya M, Kushiro T, Ebizuka Y.** Dammarenediol-II synthase, the first dedicated enzyme for ginsenoside biosynthesis, in Panax ginseng. FEBS Lett. 2006 Oct 2;580(22):5143–9.

[30]. **Park S-B, Chun J-H, Ban Y-W, Han JY, Choi YE.** Alteration of Panax ginseng saponin composition by overexpression and RNA interference of the protopanaxadiol 6-hydroxylase gene (CYP716A53v2). J Ginseng Res. 2016 Jan;40(1):47–54.

[31]. **Xu J, Chu Y, Liao B, Xiao S, Yin Q, Bai R, et al.** Panax ginseng genome examination for ginsenoside biosynthesis. GigaScience. 2017 Oct 5;6(11):1–15.

[32]. **Jung S-C, Kim W, Park SC, Jeong J, Park MK, Lim S, et al.** Two ginseng UDP-glycosyltransferases synthesize ginsenoside Rg3 and Rd. Plant Cell Physiol. 2014 Dec;55(12):2177–88.

[33]. Natural Health Product. Monograph - **American ginseng. Health Canada; 2015.**

[34]. **Motsch A.** Le ginseng d'Amérique : un lien entre les deux Indes, entre curiosité et science. Études Épistémè Rev Litt Civilis XVIe – XVIIIe Siècles [Internet]. 2014 Dec 1 [cited 2016 Dec 19];(26). Available from: https://episteme.revues.org/331

[35]. **MDidea Brand**. History and modern use of American ginseng [Internet]. 2018 [cited 2018 Feb 22]. Available from: https://www.mdidea.com/products/proper/proper00506.html

[36]. **Hsu P.** Why Chinese prefer American ginseng and how they use it. In Lexington, KY, USA; 1979.

[37]. Club des Producteurs de Ginseng de la Vallée de la Gatineau. Information bulletin - Volume 6 - Number 1 - Fall 2016. 2016.

[38]. **Mancuso C, Santangelo R.** Panax ginseng and Panax quinquefolius: from pharmacology to toxicology. Food Chem Toxicol. 2017 Sep 1;107:362–72.

[39]. **Qi L-W, Wang C-Z, Yuan C-S.** American ginseng: potential structure–function relationship in cancer chemoprevention. Biochem Pharmacol. 2010 Oct 1;80(7):947–54.

[40]. **Vogler BK, Pittler MH, Ernst E.** The efficacy of ginseng. A systematic review of randomised clinical trials. Eur J Clin Pharmacol. 1999;55:567–75.

[41]. **Wang C-Z, Yuan C-S**. Potential role of ginseng in the treatment of colorectal cancer. Am J Chin Med. 2008;36(06):1019–1028.

[42]. **Wu Z, Luo J, Luo L.** American ginseng modulates pancreatic beta cell activities. Chin Med. 2007;2(1):11.

[43]. **Yarnell E, Abascal K. Herbs for Diabetes: Update—Part 1.** Altern Complement Ther. 2014 Dec;20(6):328–33.

[44]. **Ghorbani A.** Best herbs for managing diabetes: a review of clinical studies. Braz J Pharm Sci. 2013 Sep;49(3):413–22.

[45]. **Mucalo I, Rahelic D, Jovanovski E, Bozikov V, Romic Z, Vuksan V.** Effect of American ginseng (Panax quinquefolius L.) on glycemic control in type 2 diabetes. Coll Antropol. 2012;36(4):1435–1440.

[46]. **Xie J-T, Mehendale S, Yuan C-S.** Ginseng and diabetes. Am J Chin Med. 2005;33(03):397–404.

[47]. **Xie J-T, Mehendale SR, Wang A, Han AH, Wu JA, Osinski J, et al.** American ginseng leaf: ginsenoside analysis and hypoglycemic activity. Pharmacol Res. 2004 Feb 1;49(2):113–7.

[48]. **Xie JT, Wu JA, Mehendale S, Aung HH, Yuan C-S.** Anti-hyperglycemic effect of the polysaccharides fraction from American ginseng berry extract in ob/ob mice. Phytomedicine. 2004 Jan 1;11(2):182–7.

[49]. **Vuksan V, Sievenpiper JL, Koo VYY, Francis T, Beljan-Zdravkovic U, Xu Z, et al.** American ginseng (Panax quinquefolius L) reduces postprandial glycemia in nondiabetic subjects and subjects with type 2 diabetes mellitus. Arch Intern Med. 2000 Apr 10;160(7):1009.

[50]. **Sen S, Chen S, Feng B, Wu Y, Lui E, Chakrabarti S.** Preventive effects of North American ginseng (Panax quinquefolium) on diabetic nephropathy. Phytomedicine. 2012 Apr 15;19(6):494–505.

[51]. **Jenkins AL, Morgan LM, Bishop J, Jovanovski E, Jenkins DJA, Vuksan V.** Co-administration of a konjac-based fibre blend and American ginseng (Panax quinquefolius L.) on glycaemic control and serum lipids in type 2 diabetes: a randomized controlled, cross-over clinical trial. Eur J Nutr [Internet]. 2017 Jul 7 [cited 2018 Feb 12]; Available from: http://link.springer.com/10.1007/s00394-017-1496-x

[52]. **Mucalo I, Jovanovski E, Rahelić D, Božikov V, Romić Ž, Vuksan V.** Effect of American ginseng (Panax quinquefolius L.) on arterial stiffness in subjects with type-2 diabetes and concomitant hypertension. J Ethnopharmacol. 2013 Oct 28;150(1):148–53.

[53]. **Mucalo I, Jovanovski E, Vuksan V, Božikov V, Romić Ž, Rahelić D.** American ginseng extract (Panax quinquefolius L.) is safe in long-term use in type 2 diabetic patients. Evid Based Complement Alternat Med [Internet]. 2014 [cited 2017 Nov 10];2014. Available from: https://www.hindawi.com/journals/ecam /2014/969168/

[54]. **Peralta EA, Murphy LL, Louis S, Minnis J, Dunnington GL.** American ginseng inhibits induced COX-2 and NFKB activation in human breast cancer cells. J Surg Res. 2009 Feb 1;151(2):192.

[55]. **Wang C-Z, Aung HH, Zhang B, Sun S, Li X-L, He H, et al.** Chemopreventive effects of heat-processed Panax quinquefolius root on human breast cancer cells. Anticancer Res. 2008;28(5A):2545–2551.

[56]. **Park E-H, Kim Y-J, Yamabe N, Park S-H, Kim H, Jang H-J, et al.** Stereospecific anticancer effects of ginsenoside Rg3 epimers isolated from heat-processed American ginseng on human gastric cancer cell. J Ginseng Res. 2014 Jan 1;38(1):22–7.

[57]. **Aung HH, Mehendale SR, Wang CZ, Xie J-T, McEntee E, Yuan C-S.** Cisplatin's tumoricidal effect on human breast carcinoma MCF-7 cells was not attenuated by American ginseng. Cancer Chemother Pharmacol. 2006 Dec 20;59(3):369–74.

[58]. **Lee SD, Yoo G, Chae HJ, In M-J, Oh N-S, Hwang YK, et al.** Lipid-soluble extracts as the main source of anticancer activity in ginseng and ginseng marc. J Am Oil Chem Soc. 2009 Nov;86(11):1065–71

[59]. **Deng S, Wong CKC, Lai H-C, Wong AST.** Ginsenoside-Rb1 targets chemotherapy-resistant ovarian cancer stem cells via simultaneous inhibition of Wnt/β-catenin signaling and epithelial-to-mesenchymal transition. Oncotarget. 2017;8(16):25897.

[60]. **Gao J-L, Lv G-Y, He B-C, Zhang B-Q, Zhang H, Wang N, et al.** Ginseng saponin metabolite 20(S)-protopanaxadiol inhibits tumor growth by targeting multiple cancer signaling pathways. Oncol Rep. 2013 Jul;30(1):292–8.

[61]. **Li B, Wang C-Z, He T-C, Yuan C-S, Du W.** Antioxidants potentiate American ginseng-induced killing of colorectal cancer cells. Cancer Lett. 2010 Mar 1;289(1):62–70.

[62]. **Saw CL-L, Wu Q, Kong A-N.** Anti-cancer and potential chemopreventive actions of ginseng by activating Nrf2 (NFE2L2) anti-oxidative stress/anti-inflammatory pathways. Chin Med. 2010;5(1):37.

[63]. **Qi B, Liu L, Zhang H, Zhou G, Wang S, Duan X, et al.** Anti-fatigue effects of proteins isolated from Panax quinquefolium. J Ethnopharmacol. 2014 Apr 28;153(2):430–4.

[64]. **Tang K, Nie R, Jing L, Chen Q.** Anti-athletic fatigue activity of saponins (ginsenosides) from American ginseng (Panax quinquefolium L.). Afr J Pharm Pharmacol. 2009;3(6):301–6.

[65]. **Barton DL, Soori GS, Bauer BA, Sloan JA, Johnson PA, Figueras C, et al.** Pilot study of Panax quinquefolius (American ginseng) to improve cancer-related fatigue: a randomized, double-blind, dose-finding evaluation: NCCTG trial N03CA. Support Care Cancer. 2010 Feb;18(2):179–87.

[66]. **Lu K-H, Weng C-Y, Chen W-C, Sheen L-Y.** Ginseng essence, a medicinal and edible herbal formulation, ameliorates carbon tetrachloride-induced oxidative stress and liver injury in rats. J Ginseng Res. 2017 Jul;41(3):316–25.

[67]. **Garbett J, Wilson SAF, Ralston JC, De Boer AA, Lui EMK, Wright DC, et al.** North American ginseng influences adipocyte–macrophage crosstalk regulation of inflammatory gene expression. J Ginseng Res. 2016 Apr;40(2):141–50.

[68]. **Wilson SAF, Wong MHT, Stryjecki C, De Boer A, Lui EMK, Mutch DM.** Unraveling the adipocyte inflammomodulatory pathways activated by North American ginseng. Int J Obes. 2013 Mar;37(3):350–6.

[69]. **Estaki M, Noble EG.** North American ginseng protects against muscle damage and reduces neutrophil infiltration after an acute bout of downhill running in rats. Appl Physiol Nutr Metab. 2015 Feb;40(2):116–21.

[70]. **Xie J-J, Chen J, Guo S-K, Gu Y-T, Yan Y-Z, Guo W-J, et al.** Panax quinquefolium saponin inhibits endoplasmic reticulum stress-induced apoptosis and the associated inflammatory response in chondrocytes and attenuates the progression of osteoarthritis in rat. Biomed Pharmacother. 2018 Jan 1;97:886–94.

[71]. **Wang L, Yu X, Yang X, Li Y, Yao Y, Lui EMK, et al.** Structural and anti-inflammatory characterization of a novel neutral polysaccharide from North American ginseng (Panax quinquefolius). Int J Biol Macromol. 2015 Mar 1;74:12–7.

[72]. **Kitts DD, Wijewickreme AN, Hu C.** Antioxidant properties of a North American ginseng extract. Mol Cell Biochem. 2000;203(1–2):1–10.

[73]. **Yu X, Yang X, Cui B, Wang L, Ren G.** Antioxidant and immunoregulatory activity of alkali-extractable polysaccharides from North American ginseng. Int J Biol Macromol. 2014 Apr 1;65:357–61.

[74]. **Lee T, Wang W, O'Brien K, Johnke R, Wang T, Allison R.** Effect of American ginseng on total antioxidant capacity and reactive oxygen species of human lymphocytes before and after 137Cs-irradiation. Int J Radiat Oncol. 2008 Sep 1;72(1, Supplement):S702.

[75]. **Li J, Ichikawa T, Jin Y, Hofseth LJ, Nagarkatti P, Nagarkatti M, et al.** An essential role of Nrf2 in American ginseng-mediated anti-oxidative actions in cardiomyocytes. J Ethnopharmacol. 2010 Jul 20;130(2):222–30.

[76]. **Shao Z-H, Xie J-T, Vanden Hoek TL, Mehendale S, Aung H, Li C-Q, et al.** Antioxidant effects of American ginseng berry extract in cardiomyocytes exposed to acute oxidant stress. Biochim Biophys Acta BBA - Gen Subj. 2004 Feb 24;1670(3):165–71.

[77]. **Wu Y, Lu X, Xiang F-L, Lui EMK, Feng Q.** North American ginseng protects the heart from ischemia and reperfusion injury via upregulation of endothelial nitric oxide synthase. Pharmacol Res. 2011 Sep 1;64(3):195–202.

[78]. **Scholey A, Ossoukhova A, Owen L, Ibarra A, Pipingas A, He K, et al.** Effects of American ginseng (Panax quinquefolius) on neurocognitive function: an acute, randomised, double-blind, placebo-controlled, crossover study. Psychopharmacology (Berl). 2010 Oct;212(3):345–56.

[79]. **Shin K, Guo H, Cha Y, Ban Y-H, Seo DW, Choi Y, et al.** CereboostTM, an American ginseng extract, improves cognitive function via up-regulation of choline acetyltransferase expression and neuroprotection. Regul Toxicol Pharmacol. 2016 Jul;78:53–8.

[80]. **Kumar A**. Possible nitric oxide modulatory mechanism of American ginseng against chronic unpredictable stress-induced cognitive impairment, neuroinflammation, and biochemical alterations. Alzheimers Dement. 2017 Jul 1;13(7, Supplement):P622.

[81]. **González-Burgos E, Fernandez-Moriano C, Gómez-Serranillos MP.** Potential neuroprotective activity of ginseng in Parkinson's disease: a review. J Neuroimmune Pharmacol. 2015 Mar;10(1):14–29.

[82]. **Qi B, Wang S, Wang Q, Zhang H, Bai X, He H, et al.** Characterization and immunostimulating effects on murine peritoneal macrophages of a novel protein isolated from Panax quinquefolius L. J Ethnopharmacol. 2016 Dec 4;193:700–5.

[83]. **Azike CG, Charpentier PA, Hou J, Pei H, Lui EMK.** The Yin and Yang actions of North American ginseng root in modulating the immune function of macrophages. Chin Med. 2011;6(1):21.

[84]. **Lui EMK, Azike CG, Guerrero-Analco JA, Romeh A, Pei H, Kaldas SJ, et al.** Bioactive polysaccharides of American ginseng Panax quinquefolius L. in modulation of immune function: phytochemical and pharmacological characterization. In: Karunaratne DN, editor. The Complex World of Polysaccharides [Internet]. InTech; 2012 [cited 2018 Feb 12]. Available from: http://www.intechopen.com/books/the-complex-world-of-polysaccharides/bioactive-polysaccharides-of-american-ginseng-panax-quinquefolius-l-in-modulation-of-immune-function

[85]. **Rinwa P, Kumar A.** Modulation of nitrergic signalling pathway by American ginseng attenuates chronic unpredictable stress-induced cognitive impairment, neuroinflammation, and biochemical alterations. Naunyn Schmiedebergs Arch Pharmacol. 2014 Feb;387(2):129–41.

[86]. **Wilson SA, Stryjecki C, De Boer A, Lui E, Mutch DM.** Immunomodulatory activity of North American ginseng in 3T3-L1 adipocytes. Can J Diabetes. 2011 Jan 1;35(2):173.

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