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Review Article

Pharmacological and Clinical Efficacy of American Ginseng (*Panax Quinquefolius*): A Mini Review

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Abstract: American Ginseng (*Panax quinquefolius*, AG) is a standout amongst the most perceived herbal botanicals in Oriental Medicine and the alternative healthcare market. In spite of the fact that AG is not as broadly studied as *Panax Ginseng*, none the less, AG is one of the best-selling herbs in the world market, and has gathered expanding attention from researchers as of late. AG is grown in the United States of America, Canada, and The People's Republic of China, on subject of AG industry and quality standards Wisconsin Ginseng is considered to be the gold standard for the highest quality grown worldwide. AG has been farmed in Wisconsin, U.S., for more than 100 years, dating back to the 1800's which birthed the artificially propagated industry. Today, Wisconsin Ginseng farmers account for 95 percent of the total cultivated AG production of the United States which continues to attract the studies of researcher professionals to the environmentally clean and regulated grown Wisconsin source of origin. Ongoing studies have demonstrated that through the numerous unregulated cultivated procedures that AG is grown, fungal molds, pesticides, and various metals and residues have contaminated the crops. Scientific investigations of AG in the past decade have increased drastically due to the increasing demand of herbal derived biomedicines from natural botanical plant sources that have demonstrated significant potential in clinical efficacy of important diseases. AG Past studies demonstrated have shown ginseng saponins called ginsenosides are the major active constituents in AG. The investigations of AG were relatively limited in the previous decade, but some encouraging advances have been accomplished in understanding the chemistry, pharmacology and structure-function relationship of AG and its clinical efficacy. In this manner, we review pharmacological effects of the ginsenosides, also the clinical efficacy on the cardiovascular system, immune system, and nervous system as well as metabolism and anti-cancer effects. Concentrating on the clinical evidence has indicated particular effectiveness in specific diseases, such as diabetes mellitus, arterial stiffness, neurocognitive disorders, and cancer fatigue as a recommended adjunct treatment along with supplementing conventional therapy.

Keywords: American Ginseng, *Panax quinquefolius*, Ginsenosides, Pharmacological Efficacy, Clinical Efficacy

1. Introduction

The artificially propagated American Ginseng (*Panax quinquefolius* [AG]) Pharmaceutical name *Radix Panacis Quinquefolii* is grown in the United States of America, Canada, and The People's Republic of China, AG is listed in Appendix II of the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) [1]. More than 90% of the cultivated ginseng grown in the United States is grown in state of Wisconsin and is considered the "gold standard" of AG worldwide. Due to the science advancements of trace metal concentrations for forensic comparison of geographical origins, this advancement in science has led to being able to decipher the country of origin and source to which the AG was grown is in now traceable [3]. This brake through has the potential to advance scientific investigations

of effects the growing environment and regulated farming methods have on the plants potency and safety. The origin of AG for medical purpose use in East Asian has over 1000 years of history, the botanical plants international trade began in the mid-1700s [1, 4, 5] to East Asia for Oriental Medicine clinical treatment of a wide verity of pathologies due to AG's pharmacological properties, a traditional medical practice that continues to this day in the far eastern and the western worlds of Integrative medicine [4-7]. AG was first introduced in the "New Compilation of Materia Medica" in 1757 [8].

Past investigations of AG, revealed to reduce stress, lower high blood sugar, increase sex drive, memory and learning abilities, decrease aging and adjust immunity [9]. The medical research of AG is conducted with the majority of studies focusing on the bioactive compounds called ginseng ginsenosides or saponins [11-13], AG is also said to be referred to as a tonic in Oriental Medicine and an adaptogen in other practices of herbal alternative medicine [11, 14-16]. AG Pharmacological efficacy studies in the basic research field revealed ginsenosides effects on the nervous system, cardiovascular system, immune system, metabolism, cancer, cellular stress response [10, 17]. Past studies have led to the discovery of the effects of AG ginsenosides on anti-aging, anti-cancer, anti-stress, and anti-fatigue [18, 19]. The majority of AG clinical investigation studies have been done on type 2 diabetes, cancer-related fatigue, Neurocognitive function, and oxidative effects [20-23]. The aim of this review is to discuss past findings of AG to increase awareness of the evidence supporting AG's pharmacological and clinical efficacy and to support the past conducted research that the adjunct treatment of important diseases along with supplementing conventional treatment of AG is a safe and effective means.

2. Materials and Method

The data source and selection was done by a query of the PubMed Web site (https://www.ncbi.nlm.nih.gov/pubmed) was conducted by applying an advanced search function with "American ginseng or *Panax quinquefolius*" for "Pharmacological efficacy" and "clinical efficacy" very few articles were extracted from other sources. To be eligible, a study should have a description of using AG or *Panax quinquefolius* as a monopreparation as the research in the studies records, studies for all indications were included. Studies were excluded if the intervention or base of research was not component contained in or of the AG plant.

3. Chemistry

The bioactive components of AG are ginseng ginsenosides or triterpenoid saponins based on their glycosylation patterns which main groups are classified as either 20(S)-protopanaxatriol (PPD) known as, Ra1, Ra2, Ra3, Rb1, Rh2, Rb3, Rc, Rd, 20(S)-Rg3, Rb2, quinoquenosides (Q)-R1, Rs1, Rs2, malonyls (MA)-Rb1, MA-Rb2, MA-Rc, MA-Rd, Rg3, etc., and 20(S)-protopanaxadiol (PPT) known as Re, Rf, Rg1, Rg2, Rh1, 20-glucopyranosyl (Glc)-Rf, r-R1, 20R-Rg2, 20R-Rh1, etc., oleanolic acid (Ro), and ocotillol (P-F11, R15) types [19, 24-30]. Other important chemical constituents of AG include polyacetylenes, sesquiterpenes, polysaccharides, and peptidoglycans, have also been isolated along with volatile constituents, organic acids, amino acids, sugars, and other constituents [12, 14]. More than 150 ginsenosides have been isolated from different parts of the AG plant so far [31]. The majority of AG ginsenosides are Rb1 (1.51%), Re (0.89%), Rd (0.77%), in AG is several times higher than they are in *Panax ginseng* [28]. Rb1>Re>Rg1=Rc>Rd, and these five ginsenosides account for approximately more or less than 70% of total ginsenosides in AG [25, 33, 34] which is a AG differentiation from *Panax ginseng* another example is 24(R)-pseudoginsenoside F11 content is approximately 0.1% in AG, and approximately 0.0001% in *Panax ginseng* according to previous AG studies. Ginsenosides from ginseng are divided into several groups (Figure 1) [14], Ginsenosides characterized from American ginseng. PPD, protopanaxadiol; PPT, protopanaxatriol; G, ginsenoside; Q, quinquenoside; F, floralquinquenoside; NG, notoginsenoside; QF, quinquefoloside (Figure 2) [171].

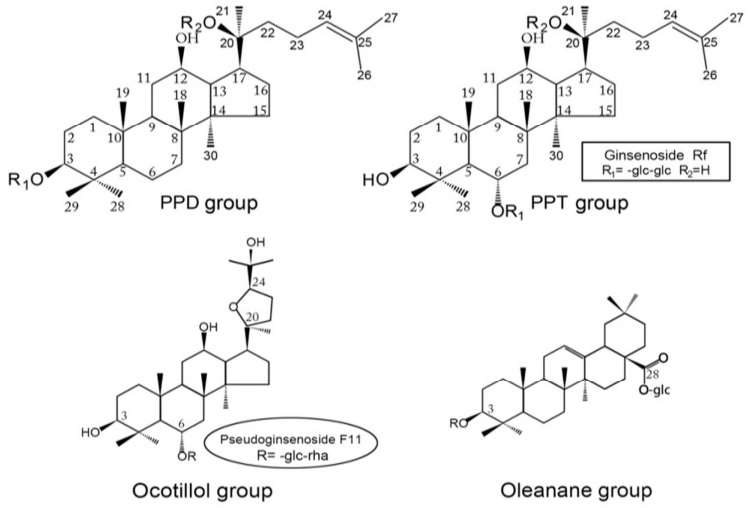
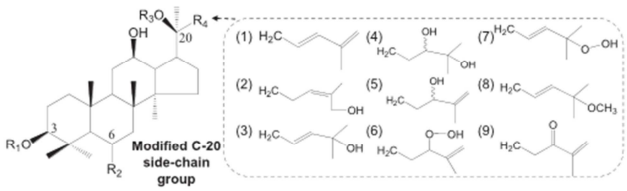
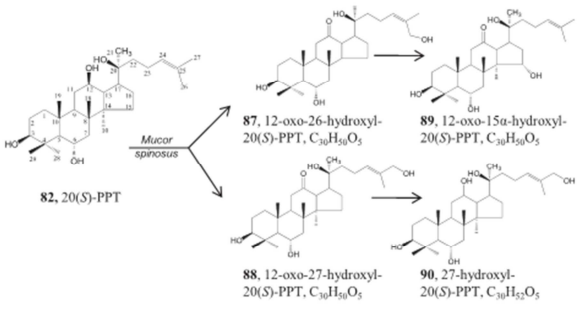
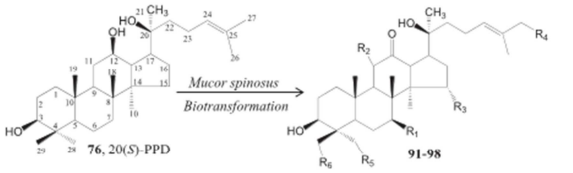


Figure 1. *Core chemical structures of four types of triterpenoid saponins from ginseng, i.e., protopanaxadiol (PPD) group, protopanaxatriol (PPT) group, ocotillol group, and oleanane group. Ginsenoside Rf (in square) is uniquely present in Asian ginseng, and pseudoginsenoside F11 (in circle) is uniquely present in AG [14].*

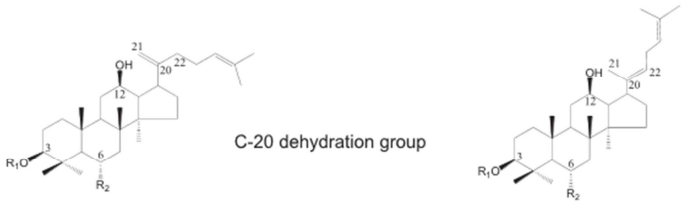


No	Saponin	R_1	R_2	R_3	R_4	Formula
42	Q-L_1	glc^2→glc	H	glc	(1)	$C_{48}H_{80}O_{18}$
43	Q-L_8	glc	H	glc^6→xyl	(1)	$C_{47}H_{78}O_{17}$
44	Q-L_2	glc^2→glc	H	glc	(2)	$C_{48}H_{82}O_{19}$
45	Q-L_{11}	H	*O*-glc^2→rha	H	(2)	$C_{42}H_{72}O_{14}$
46	Q-L_3	glc	H	glc^6→xyl	(3)	$C_{47}H_{80}O_{18}$
47	Q-L_7	glc^2→glc	H	glc^6→xyl	(3)	$C_{53}H_{90}O_{23}$
48	NG-A	glc^2→glc	H	glc^6→glc	(3)	$C_{54}H_{92}O_{24}$
49	Gypenoside LXIX	glc^2→glc	H	glc^6→xyl	(3)	$C_{53}H_{90}O_{23}$
50	Vina-G-R_8	glc^2→glc	H	glc	(3)	$C_{48}H_{82}O_{19}$
51	Q-L_9	H	*O*-glc^2→rha	H	(4)	$C_{42}H_{74}O_{15}$
52	Q-L_{16}	glc^2→glc	H	glc^6→glc	(4)	$C_{54}H_{94}O_{25}$
53	Gypenoside LXXI	glc^2→glc	H	glc^6→glc	(5)	$C_{53}H_{90}O_{23}$
54	Majoroside-F_1	glc^2→glc	H	glc	(5)	$C_{48}H_{82}O_{19}$
55	NG-C	glc^2→glc	H	glc^6→glc	(6)	$C_{54}H_{92}O_{25}$
56	G-I	glc^2→glc	H	glc	(6)	$C_{48}H_{82}O_{20}$
57	F-B	H	*O*-glc^2→rha	H	(6)	$C_{42}H_{72}O_{15}$
58	F-D	glc	H	glc	(6)	$C_{42}H_{72}O_{15}$
59	NG-E	glc^2→glc	H	glc	(7)	$C_{48}H_{82}O_{20}$
60	NG-K	glc^2→glc	H	glc^6→glc	(7)	$C_{54}H_{92}O_{25}$
61	F-A	H	*O*-glc	H	(7)	$C_{36}H_{62}O_{11}$
62	F-C	H	*O*-glc^2→rha	H	(7)	$C_{42}H_{72}O_{15}$
63	QF-L_a	glc^2→glc	H	glc^6→arap	(8)	$C_{54}H_{92}O_{23}$
64	QF-L_c	glc^2→glc	H	glc^6→xyl	(8)	$C_{54}H_{92}O_{23}$
65	G-III	glc^2→glc	H	glc	(9)	$C_{48}H_{80}O_{19}$





No	Saponin	R_1	R_2	R_3	R_4	R_5	R_6	Formula
91	12-oxo-15α,27-dihydroxyl-20(*S*)-PPD	H	H	OH	OH	H	H	$C_{30}H_{50}O_5$
92	12-oxo-7β,11α,28-trihydroxyl-20(*S*)-PPD	OH	OH	H	H	OH	H	$C_{30}H_{50}O_6$
93	12-oxo-7β,28-dihydroxyl-20(*S*)-PPD	OH	H	H	H	OH	H	$C_{30}H_{50}O_5$
94	12-oxo-15α,29-dihydroxyl-20(*S*)-PPD	H	H	OH	H	H	OH	$C_{30}H_{50}O_5$
95	12-oxo-7β,15α-dihydroxyl-20(*S*)-PPD	OH	H	OH	H	H	H	$C_{30}H_{50}O_5$
96	12-oxo-7β,11β-dihydroxyl-20(*S*)-PPD	OH	OH	H	H	H	H	$C_{30}H_{50}O_5$
97	12-oxo-15α-hydroxyl-20(*S*)-PPD	H	H	OH	H	H	H	$C_{30}H_{50}O_4$
98	12-oxo-7β-hydroxyl-20(*S*)-PPD	OH	H	H	H	H	H	$C_{30}H_{50}O_4$



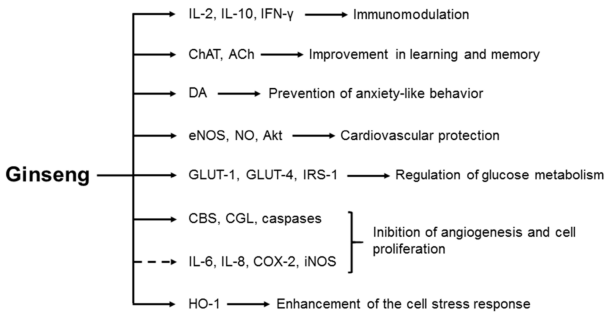
No	Saponin	R_1	R_2	Formula
70	G-Rk_3	H	*O*-glc	$C_{36}H_{60}O_8$
72	G-Rk_1	glc^2→glc	H	$C_{42}H_{70}O_{12}$
80	G-Rk_2	glc	H	$C_{36}H_{60}O_7$
78	20-dehydr-PPD	H	H	$C_{30}H_{50}O_2$
84	20-dehydr-PPT	H	OH	$C_{30}H_{50}O_3$

No	Saponin	R_1	R_2	Formula
71	G-Rh_4	H	*O*-glc	$C_{48}H_{76}O_{19}$
73	G-Rg_5	glc^2→glc	H	$C_{42}H_{66}O_{14}$
81	G-Rh_3	glc	H	$C_{36}H_{60}O_7$
79	20-dehydr-PPD	H	H	$C_{30}H_{50}O_2$
85	20-dehydr-PPT	H	OH	$C_{30}H_{50}O_3$

Figure 2. *Ginsenosides characterized from American ginseng [171].*

4. Pre-clinical Efficacy

In this section we report on recent preclinical basic research done on the AG's various pharmacological effects. Although AG's ginsenosides types are abundant with multiple pharmacological effects the major ginsenoside composition of the plant is Rb1, Re, Rd [25, 33, 34] the other ginsenoside compounds the make up the lessor composition of AG also has important pharmacological effects of their own. The AG Oriental Medicine pharmacological properties are cold, sweet, slightly bitter with the key characteristics that tonify both the qi and yin, cool fire from yin deficiency, recommend dosage 3-6 grams [6, 14]. AG's various pharmacological effects have been summarized in "Table 1" and (Figure 3) [17].



Straight arrow, increase/stimulation; dashed arrow, decrease/inhibition.

Figure 3. *Some of the main intracellular targets involved in the pharmacological effects of ginseng.*

ACh, acetylcholine; CBS, cystathionine-b-synthase; CGL, cystathionine-g-lyase; ChAT, choline acetyl transferase; COX-2, cyclooxygenase-2; DA, dopamine; eNOS, endothelial nitric oxide synthase; GLUT, glucose transporter; HO-1, heme oxygenase-1; IFN, interferon; IL, interleukin; iNOS, inducible nitric oxide synthase; IRS-1, insulin receptor substrate-1 [17].

Table 1. *Data from studies deemed low quality or results insignificant were excluded.*

Origins	Administration procedures	Pharmacological action	Subjects	References
Crude extract	Extract variant	Glycemic control	Human	[20]
Crude extract	Extract variant	Improves cardiac function	Mice	[88]
Crude extract	Extract variant	Recovered cognitive function	Mice	[74]
Crude extract	Extract variant	Acute central nervous system injury	Rat	[75]
Whole root	Capsule	Cancer-related fatigue	Human	[21]
Whole root	Powder	Protect cellular DNA from oxidative stress	Human	[157]
Whole root	Novel protein	Promoting immune function and metabolism	Murine	[49]
		Suppressive effects on proinflammatory responses	Cell	[37]
		Prevent memory shortages	Rat	[55]
	Rb1	Cardioprotective	Mice	[83]
		Anti-diabetic and insulin-sensitizing activities	Cell	[100]
Single compound		Increases the T-helper cell and stimulates immune activity	Rat	[36]
		Stimulatory effects on CNS	Rat	[53]
	Rg1	Protects cardiomyocytes	Cell	[78]
		Reduce blood glucose levels	Cell	[162]
	Re	Protects human umbilical vein endothelial cells against oxidative stress damage	Cell	[32]

4.1. Effects on the Immune System

Past investigations into AG have shown the stimulation effects on the immune system, Rb1 inhibits leukotriene release, Rg1 increases the T-helper cell and stimulates immune activity, polysaccharide and PPT type ginsenosides enhance interferon production, phagocytosis, natural killer cells, B and T cells [36]. The Rb1, Rg1 and Rg3 contained in AG inhibit cytokine production, inhibit COX-2 gene expression, inhibit histamine release, stabilize neutrophils and lymphocytes [10, 37-41]. AG's extract concentrate appeared to be a potential radiation countermeasure on human peripheral blood lymphocytes administered as a dietary supplement [42]. AG's extract concentrate had a dependable, positive quantitative effect on the lymphocytes and monocytes in mice [43]. AG increased the number of natural killer cells in mice spleen and bone marrow [44]. Particular groups of immune cells reacted to AG intervention and immunocompromised cells were more probable directed by AG treatment on mice [45]. Bioassay investigations affirmed that compound 7 demonstrated an additional immunosuppressive action towards inhibiting the production of nitric oxide and tumor necrosis factor alpha in lipopolysaccharide-induced macrophage cells in a measurements subordinate way utilizing murine macrophages [46]. The polysaccharides of AG exerted immunostimulant and suppressed lipopolysaccharide immune response under basal and lipopolysaccharide actuated proinflammatory conditions in lab rats [47]. Strikingly, compound K (40 mg/kg and 160 mg/kg per os) exerted an anti-inflammatory effect by suppressing memory B cell subsets, CD40L expression on T cells and CD40 expression on B cells in a lab rat model of adjuvant induced arthritis [48]. Immunological investigations showed that AG could prominently expand phagocytosis of macrophages, encourage nitric oxide generation, Tumor necrosis factor-α and interleukin-6 creation. Additionally, AGNP measurement dose-dependently stimulated NO development through the up-regulation of iNOS action, immunoregulatory effects [49].

4.2. Effects on the Nervous System

Ginseng has both stimulatory and inhibitory effects on the central nervous system (CNS), and may balance neurotransmission, likewise gainful beneficial effects on aging, CNS disorders, and neurodegenerative diseases [50]. Ginsenosides are responsible for ginseng's effects on the central nervous system (CNS), the peripheral nervous system, and [51]. One of AG's properties in Oriental Medicine is that of "cold" which is similar to the effect of calming to the CNS in Biomedicine science [6, 14, 52]. AG Rg1 and Rb1 enhance CNS activities, but the effect of Rb1 is inhibitory when compared to Rg1 as having stimulatory effects on CNS, AG has a higher ratio of Rb1 to Rg1 relevant correlation to the Oriental Medicine properties of "cold" or calming to the CNS [6, 14]. The protective effects of Rb1, Rg1, Rg3 and Rh2 on neurodegeneration are well investigated in past animals and in neuronal cell cultures studies [16, 51, 53, 54]. Rb1 has appeared to partially prevent the memory shortages caused by the cholinergic agent scopolamine in a lab rat study [55]. Ginsenosides regulate different types of ion channels, for example, voltage-dependent and ligand-gated ion channels, in neuronal and heterologously expressed cells. Ginsenosides inhibit voltage-dependent Ca^{2+}, K^{+}, and Na^{+} channel activities in a stereospecific way. They likewise inhibit ligand-gated ion channels for example, N-methyl-d-aspartate, some subtypes of nicotinic acetylcholine, and 5-hydroxytryptamine type 3 receptors [56]. *In vivo* studies have shown that ginsenosides enhance spatial learning and increase hippocampal synaptophysin levels in mice [57], diminish infarct and neuronal deficit on transient cerebral [58], what's more, effectively attenuate Tau protein hyperphosphorylation of hippocampal neurons [59]. What's more, ginsenosides advance neurotransmitter release by increasing the phosphorylation of synapsis [60]. Competition and site-directed mutagenesis

experiments uncovered that ginsenosides communicate with ligand-binding sites or channel pore sites and inhibit open states of ion channels [53]. Past reports demonstrate that long-term ginsenoside consumption could diminish memory loss and impairment by decreasing oxidative stress and up-regulating the plasticity-related proteins in the hippocampus [61, 62]. In mice exposed to chronic unpredictable stress, the administration of an AG concentrate extract of (100-200 mg/kg per p.o. prior to the stress) reverted both corticosterone plasma levels and the stress-induced exhaustion of noradrenaline, dopamine and serotonin (5-HT) in the hippocampus and cortex by reestablishing the regulation of the stress axis and diminishing interleukin production [63]. AG Concentrate Extracts have markedly neuroprotective effects in Alzheimer's Disease cellular model on SH-SY5Y cells apoptosis induced by Abeta25-35 [64]. The beneficial effect of ginseng and ginsenosides were demonstrated on neurodegenerative disease models of Parkinson's and Alzheimer's diseases [65, 66]. AG ginsenosides were shown to enhanced cognitive performance and mood [67-70]. Long-term AG ginsenoside administration to mice prevented memory loss or diminishment [61, 62]. Corsi block and calmness showed improved after administration of American ginseng to healthy young adults [22]. AG aqueous extract significantly decreased (i) clinical signs of EAE, (ii) levels of circulating TNF-α, and (iii) central nervous system immunoreactive NOS and demyelination scores, without a change in other neuropathological measures. This investigation demonstrates that an aqueous extract of AG may have the capacity to constrict certain indications of EAE, suggesting that it may be a useful adjuvant therapy for MS [71].

The neuroprotective effect of PF11 on Parkinson's disease (PD) suggests that PF11 has potent anti-Parkinson property possibly through inhibiting free radical formation and stimulating endogenous antioxidant release [72]. Discoveries propose that modulation of nitrergic signaling cascade is associated with the protective effects of AG exact against chronic unpredictable stress CUS-induced cognitive dysfunction, oxidative stress, and neuroinflammation [73]. An AG extract concentrate standardized to 10-12% total ginsenosides, Cereboost™, at doses 30, 100 or 300 mg/kg/day per os for 16 days, expanded acetylcholine creation by up-regulating choline acetyltransferase in the brain of mice tested with amyloid-beta (Aβ) peptides (Aβ 1-42); thus, learning and memory functions significantly improved in these lab animals [74]. AG saponin treatment ameliorated the damage to spinal tissue and improved the functional recovery after spinal cord injury (SCI). AG saponin treatment inhibited endoplasmic reticulum (ER) stress and the related apoptosis after acute SCI. AG saponin additionally abolished the triglyceride (TG)-induced ER stress and associated apoptosis in neuronal cultures. AG saponin appears to inhibit the ER-stress-induced neurite injury in PC12 cells. outcomes recommend that AG saponin is a novel therapeutic agent for acute central nervous system injury [75].

4.3. Effects on the Cardiovascular System

The acute antioxidant and protective effect of AG berry extract concentrate has been shown in cultured cardiomyocytes and pretreatment with an extract concentrate up-regulating peroxide detoxifying mechanisms, which could influence intracellular oxidant dynamics [76]. Past investigations into AG observed that the extract concentrate has a stronger antioxidant activity compared to that of the Asian ginseng root (*Panax ginseng*) [76, 77]. A consequent study demonstrated that ginsenoside Re, the major constituent in the AG extract concentrate, functions as an antioxidant by protecting cardiomyocytes from damage induced by both exogenous and endogenous oxidants, the defensive effects of which might be for the most part ascribed to scavenging H2O2 and hydroxyl radicals [78]. In an acute myocardial infarction lab rat model, the effect of AG saponins demonstrate myocardium protection from ischemic damage in rats after the infarction by way of promoting angiogenesis in the affected area of myocardium and up-regulating expressions of VEGF and bFGF in myocardial cells [79]. The antioxidant saponin components of AG and their activities have been reviewed and connections between the observed effects and the chemical structures have been investigated [79-81]. In the U.S. AG is a prominent herbal supplement for patients experiencing cardiovascular disease [78, 81]. Several anti-ischemic, anti-arrhythmic and anti-hypertensive effects have been seen after the utilization of AG [81]. The pharmacological effects impacts might be delivered by the antioxidant properties of the herb [78]. The antioxidant activities and the connection between chemical compound structure and cardiovascular-protecting functions of AG have been reviewed [81]. AG root and berry extract concentrate demonstrated antioxidant and protective effects in cultured cardiomyocytes by up-regulating peroxide detoxifying mechanisms [76, 77] and activating the Nrf2 pathway [82]. AG Ginsenoside Re was one noteworthy antioxidant agent that protected cardiomyocytes by scavenging H_2O_2 and hydroxyl radicals [78]. AG extract concentrate (50 mg/kg/day per os for 7 days) diminished infarct size and myocardial apoptosis in lab mice with I/R damage via activation of eNOS [83]. Both compound K (10 mg/kg per os) and ginsenoside Rb1 (40 mg/kg per os) imitated the cardioprotective impacts talked about above, in particular they reduced infarct size, cardiomyocyte apoptosis and mitochondrial swelling in lab animal models of I/R damage the study suggests that ginseng may serve as a potential therapeutic agent to limit myocardial I/R injury [83, 84]. A lab rat study results demonstrate that AG inhibits vascular smooth muscle cell VSMC proliferation through suppressing the Jak/Stat pathway [85]. Lab rat study presented evidence of depressed cardiac contractile function by acute administration of AG extract concentrate. This acute reduction in cardiac contractile function appears to be intrinsic to the myocardium [86]. A lab mice study demonstrated that an AG extract concentrate is a specific Nrf2 activator and panaxynol-activated Nrf2 signaling is in any event mostly in charge of AG-induced health benefit in the heart [87]. AG inhibits myocardial NOX2-ERK1/2-TNF-α signaling pathway and enhances cardiac function in endotoxemia, recommending that AG may have the potential in the prevention of clinical

sepsis in lab mice [88]. AG attenuates adverse cardiac adrenergic reactions and, in this way, might be a viable effective therapy to decrease hypertrophy and heart failure associated with excessive catecholamine production [89].

4.4. Effects on Metabolism

AG has been utilized for treatment of diabetes as an adjuvant treatment and exhibited to have protective effects in type 1 and in type 2 diabetes [23, 90, 91]. The AG berry, leaf, and Re compound has been shown as an anti-diabetic [92], AG extract concentrate of roots, berries, and leaves additionally have been reported to have hypoglycemic effects in lab animal models of type 1 and type 2 diabetes [93, 94]. Also demonstrated to prevent multiple diabetic complications in both type 1 and type 2 diabetes [95, 96]. Observed effects of AG extract concentrate on metabolic parameters in lab animal studies with diabetes data demonstrated in type 1 diabetes body weight gain, increased insulin secretion, reduction of hyperglycemia, increased β-cell mass. Studies showed that in type 2 diabetes, body weight reduction, decreased insulin secretion, reduction of hyperglycemia, and Increased β-cell mass in AG extract concentrate [97].

Type 2 diabetes, representing for over 90% more or less of diabetic cases, is a syndrome with disordered metabolism of carbohydrates and lipids as a result of resistance to insulin action and impaired insulin secretion [98]. Earlier research studies showed that AG roots possess significant hypoglycemic abilities in diabetic lab mice models [99]. Ginsenoside Rb1, one of the major constituent in AG root, was found to possess anti-diabetic and insulin-sensitizing activities [100]. Antidiabetic effects of AG ginsenosides have been demonstrated in lab animal studies by Rb1 [101], Re [102], transformed compounds such as Rb2 [103], Rh2 [104], compound K [105], and the aglycone 20(*S*)-PPT shown they decreased oxidative stress [107, 108]. The AG in Rb1 empowered glucose transport in insulin-sensitive cells by advancing translocations of GLUT1 and GLUT4 by partially activating the insulin-signaling pathway [101]. In a past study, Rb1 was seen to advance glucose-stimulated insulin secretion through PKA, which augmented IRS2 expression to enhance insulin/IGF-1 signaling [109]. Heat processed AG had stronger effects than unprocessed AG in restraining advanced accumulation of glycation end products in diabetic lab rat kidney study [110]. Past studies suggest that the observed ability of AG ginsenoside Re to reduce blood glucose levels may be connected to its antioxidant effects on pancreatic beta-cells [162]. Past research suggests that oxidative stress is connected to diabetes [111, 112]. Considered to be a botanical antioxidant, AG may likewise protect against diabetes by adding to the total antioxidant defense system of the body [94]. However, since circuitous evidence suggests that the anti-diabetic effects of AG may not be connected to antioxidant activity [113], more research is required. Treatment with AG extract concentrate showed to improved Insulin-dependent diabetes mellitus and its related metabolic problems in various degrees. Moreover, it has insulin sensitizing, hypoglycemic, antioxidant and vasodilator effects. Communally AG extract concentrate is a potential method to surmount the diabetic state and it has vasodilator effects [91]. It merits bringing up that compound K and ginsenoside Rb1 are responsible for the same effects on glucose metabolism credited to AG preparations [48, 114].

4.5. Effects on Cancer

AG can conceivably be utilized for cancer treatment and chemotherapy induced side-effect management. In *in vitro* studies, AG was found to repress the growth of breast cancer cells [115, 116]. After heat processed treatment of AG, its anti-proliferative effects on cancer cells were improved significantly, perhaps due to the altered ginsenoside profile [117, 118]. Anti-proliferative effects of agent constituents were also evaluated, demonstrating that ginsenoside Rg has a constructive effect. Heat processed AG repressed the colorectal cancer growth both *in vitro* and *in vivo*, which may be accomplished through cell cycle arrest and induced apoptosis in the cells [119].

The cellular and molecular focuses of ginsenosides against cancer have additionally been examined. It appears that several molecular mechanisms exist and collectively converge on various signaling pathways. These pathways incorporate regulation of cell cycle, induction of apoptosis, inhibition of angiogenesis, prohibition of invasion, and reduction of inflammatory response [120, 121]. A progression of cell cycle proteins, apoptosis-related proteins, growth factors, protein kinases, and transcription factors are influenced by ginsenosides [120-122]. For instance, Rh2 and Rg3 hinder cancer cell proliferation by initiating gene and protein articulation of the cell cycle regulatory protein p21, accordingly arresting tumor cell cycle progression by inducing cancer cell apoptosis through activation of caspase-3 protease via a bcl-2-insensitive pathway and by sensitizing multidrug-resistant tumor cells to chemotherapy [123-125]. To describe further downstream genes targeted by ginseng saponins, for example, Rg3 in a human cancer cell line, the gene expression profiling was assayed, demonstrating that the most influenced pathway was the Ephrin receptor pathway [126].

The most generally used cancer chemotherapies are limited by extreme side effects and dose-limiting toxicity. The drug-related adverse events not only worsen patients' quality of life, as well as prompt to refusal to continue the potentially curative chemotherapy. AG's ginsenoside Re constricted cisplatin-induced nausea and vomiting in a lab rat study without affecting its anti-cancer properties in human cancer cells [127, 128]. Another studied pharmacological action of AG and its constituents is cancer chemoprevention and inhibition of tumor growth [117, 129, 130]. AG extract concentrate enhanced the chemo preventive impact of 5-fluorouracil in human colon cells, suppressed the chromosomal variation induced by mitomycin C in mice [132]. Heat processed AG has more potent activity than Asian *Panax ginseng* on human cancer cells [117, 118]. Heat processed AG berry extract concentrate suppressed colorectal cancer growth both *in vitro* and *in vivo* [119]. Improved anticancer potential outcomes from chemical degradation and transformation of

the original saponins to new compounds during the heat steaming process [117, 132]. As a result of higher aggregate ginsenoside concentration total, AG had more grounded anticancer potential than Asian *Panax ginseng* [133]. The instrument and cellular/molecular focuses of AG against cancer have been studied. Several molecular components exist and collectively converge on various signaling pathways. These pathways incorporate the regulation of the cell cycle [117], induction of apoptosis [130, 118], inhibition of angiogenesis [134, 120], preventing invasion [121], and diminishment of inflammatory response [135, 136]. Past studies shown a series of cell cycle proteins, apoptosis-related proteins, growth factors, protein kinases and interpretation factors are influenced by AG and ginsenosides [120, 121, 134, 137-139]. For instance, AG extract concentrate can selectively hinder the expression of the inducible nitric oxide synthase by means of signal transducer and activator of transcription course in inflamed macrophages [140]. A lyophilized AG extract concentrate inhibited induced cyclooxygenase-2 and NF-kappa B activation in breast cancer cells [139]. The anticancer effect of heat processed AG was enhanced by antioxidants or inhibitors of the NF-kappa B pathway [141]. Since tumor malignancy is a complex interaction among genes, cells, and tissues [142], there are presumably numerous unknowns in the anticancer mechanisms of AG. Due to complex chemical composition and difficulty in reproducibility, most studies focus on individual ginsenosides but not AG extract concentrate. Hence, more scientific clinical trials are needed to test the effects of AG and heat processed AG against cancer.

The most recent AG study's findings suggest that AG keeps the colon environment in metabolic equilibrium when lab mice were treated with azoxymethane and dextran sulfate sodium and gives insight into the mechanisms by which AG protects from colon cancer associated with colitis [143]. Heat processed AG suppresses colitis and associated colon cancer, and mutation in p53 is seen in many colitis-driven colon cancers. In this way, heat processed AG may be extremely effective in focusing on the inflammatory cells and cancer cells since it instigates apoptosis of inflammatory cells and cell cycle arrest in both p53-/- and WT p53 colon cancer cells [144]. The molecular components of AG have anti-inflammatory properties and drives inflammatory cell apoptosis *in vivo* that suppress colitis and prevent colon cancer associated with colitis in lab mice [145]. A hexane solvent fraction of AG suppressed colitis and associated colon cancer in a dextran sulfate sodium lab mouse model study, posed via anti-inflammatory and proapoptotic mechanisms [146]. Results are consistent with an *in vitro* data and with the hypothesis that the hexane fraction of AG has anti-inflammatory properties and drives inflammatory cell apoptosis *in vivo*, providing a mechanism by which this fraction protects from colitis in this dextran sodium sulfate lab mouse model study [145]. Heat processed AG and ginsenoside gut microbiome metabolites demonstrated critical increases in cancer chemo preventive effects [147]. A study supports the understanding that targeting MMP-2 by miR-29b is an instrument by which heat processed AG suppresses the migration of colon cancer cells [148]. Heat-processing serves as an expansion in the antitumor activity of AG in human gastric cancer cells, and ginsenoside 20(S)-Rg3, the active component produced by heat-processing, incites the activation of caspase-3, caspase-8, and caspase-9, which adds to the apoptotic cell death [149]. Link observed effects to the actions of the gut microbiome in converting the parent ginsenosides to bioactive AG metabolites. Study data suggest that AG may have potential value in Colorectal cancer chemoprevention [150]. Further results suggest that the Colorectal cancer chemo preventive effects of AG are intervened through enteric microbiome population-shift recovery and dysbiosis restoration. Ginseng's control of the microbiome balance contributes to the maintenance of enteric homeostasis. Cancer chemo preventive effects of AG treatment fundamentally extended the life span of the Apc(Min/+) lab mouse. Significant alterations of metabolites including amino acids, organic acids, fatty acids, and carbohydrates were observed in Apc(Min/+) mouse in sera, which were attenuated by American ginseng treatment and simultaneous with the histopathological improvement with significantly decreased tumor initiation, progression and gut inflammation [152]. AG extract concentrate significantly decreased an azoxymethane / dextran sulfate sodium-induced colitis and colon carcinogenesis by restraining inflammatory cytokines and reestablishing the metabolomics and microbiota profiles accordingly. Selective endogenous small molecules could be utilized as biomarkers to clarify the effects of AG treatment [153]. AG was shown to with the possibility to regulate the angiogenesis at the transcriptional, translational and protein signaling level via various different mechanisms, AG could end up being an effective in cancer therapeutics [154]. A recent study indicates that the mechanical and morphological properties of AG can be utilized as the apoptotic characteristics of hepatocellular carcinoma cells. Additionally, the expanded surface roughness and elastic modulus of cells under the AG extract concentrate treatment have demonstrated that the apoptosis of hepatocellular carcinoma cells can be enhanced by AG extract concentrate. This will provide a vital implication for hepatocellular carcinoma treatment and novel drug development [155].

5. Clinical Efficacy

In a study of 1126 parents, a randomized, double-blind dose-finding 3-arm trial, 2 dosing schedules of AG extract concentrate 13 mg/kg per day on day 1, 8.5 mg/kg per day on day 2, and 4.5 mg/kg per day on day 3 with 1 placebo control during the winter months (November 2005 to March 2006) in children 3 to 12 years of age. Doses of AG were well tolerated and merit additional evaluation with regard to treatment of pediatric upper respiratory tract infection [156]. A Double-blind, randomized, placebo-controlled trial with two parallel arms. 64 patients with DSM-IV diagnosed schizophrenia, which was stable over the last 3 months, and aged between 18 and 55 years, were included, received 500

mg of dried AG extract concentrate, twice daily for 4 weeks. The main outcomes were overall cognitive function (assessed by multiple tests), working memory (including verbal and visual working memory) and clinical symptoms (measured by multiple scales) [157]. In a study that investigated the effect of AG extract concentrate, in each experiment, four different concentrations (250, 500, 750, and 1000 microg mL(-1)) of AG extract concentrate were applied to mononuclear cell cultures in RPMI 1640 90 minutes after exposure to 137Cs irradiation for CBMN assay. On DNA damage in human lymphocytes at 90 minutes post irradiation obtained from 40 healthy individuals was evaluated by cytokinesis-block micronucleus assay. Results suggest that NA extract concentrate is a relatively nontoxic natural compound that holds radioprotective potential in human lymphocytes even when applied at 90 minutes post irradiation [158]. A total of 64 individuals with well-controlled essential hypertension and type 2 diabetes. Using a double-blind, placebo-controlled, parallel design, each participant was randomized to either the selected AG extract concentrate or placebo at daily dose of 3 g for 12 weeks as an adjunct to their usual antihypertensive and anti-diabetic therapy (diet and/or medications). AI and BP were measured by applanation tonometry at baseline and after 12 weeks of treatment. Addition of AG extract concentrate to conventional therapy in diabetes with concomitant hypertension improved arterial stiffness and attenuated systolic BP, thus warrants further investigation on long-term endothelial parameters before recommended as an adjunct treatment [159]. 24 individuals living with T2DM completed a study utilizing a double-blind, cross-over design, the participants were randomized to receive either 1 g/meal (3 g/day) of AG extract concentrate or placebo for 8 weeks while maintaining their original treatment. AG significantly reduced HbA1c (− 0.29%; p = 0.041) and fasting blood glucose (− 0.71 mmol/L; p = 0.008). Furthermore, AG extract concentrate lowered systolic blood pressure (− 5.6 ± 2.7 mmHg; p < 0.001), increased NOx (+ 1.85 ± 2.13 μmol/L; p < 0.03), and produced a mean percent end-difference of − 12.3 ± 3.9% in LDL-C and − 13.9 ± 5.8% in LDL-C/HDL. AG extract concentrate added to conventional treatment provided an effective and safe adjunct in the management of T2DM [20].

A study of 32 participants followed a randomized, double-blind, placebo-controlled crossover methodology. It used multi-dose, multiple-testing-times with a (100, 200 400 mg) of Cereboost™ an AG extract concentrate processed to capsules of 10.65% ginsenosides. For Immediate Word Recall, Choice Reaction Time accuracy, Numeric Working Memory speed, Alphabetic Working Memory areas of working memory. The mean Corsi block score performance was improved by all doses at all testing times. Also self-rated calmness there was a significant main effect of treatment [22]. 52 healthy volunteers received 100mg to 200 mg of AG AG extract concentrate processed to capsules, according to a double-blind, placebo-controlled, balanced, crossover design. The Cognitive Drug Research battery and the Computerized Mental Performance Assessment System were used to evaluate cognitive performance at baseline then 1, 3 and 6 h following treatment. Blood glucose and mood were co-monitored. These data confirm that AG can acutely benefit working memory and extend the age range of this effect to middle-aged individuals [160]. In a Wisconsin *Panax quinquefolius* 290 patient's Eligible adults with cancer were accrued to this trial, randomized in a double-blind manner, to receive AG capsules in doses of 750, 1,000, or 2,000 mg/day or placebo given in twice daily dosing over 8 weeks. Outcome measures included the Brief Fatigue Inventory, vitality subscale of the Medical Outcome Scale Short Form-36 (SF-36), and the Global Impression of Benefit Scale at 4 and 8 weeks. Over twice as many patients on ginseng perceived a benefit and were satisfied with treatment over those on placebo [161]. In another Wisconsin *Panax quinquefolius* clinical trial, three hundred sixty-four participants were enrolled from 40 institutions, a multisite, double-blind trial randomized fatigued cancer survivors to 2000 mg of AG capsules vs a placebo for 8 weeks. The primary endpoint was the general subscale of the Multidimensional Fatigue Symptom Inventory– Short Form (MFSI-SF) at 4 weeks. Data support the benefit of AG, 2000mg daily, on CRF over an 8-week period. Greater benefit was reported in patients receiving active cancer treatment vs those who had completed treatment [21]. A retrospective medical record review we identified 28 patients who were prescribed a combination of methylphenidate (10-40 mg/d) and AG (2000 mg/d) capsules. Sixty percent of patients reported significant reduction in fatigue (cutoff value: ≥3; reduction in fatigue score from baseline: 80% ≥2, 60% ≥3, and 46.7% ≥4). The combination treatment of methylphenidate and AG had no discernible associated toxicities and showed potential clinical benefit in Cancer-Related Fatigue [162].

In an AG study of 14 apparently healthy volunteers. Completed slides were stained with Giemsa stain and DNA damage was assessed. The DNA protective effect trail of AG was administered by way of whole-root powder tea bag contained 1800mg AG in pieces without ''tea leaves''. The bag was infused in hot boiling water for half an hour before consumption. Tea bag had been illustrated at the cellular level by demonstrated a cup of AG infusion could protect cellular DNA from oxidative stress at least within 2 hours [163]. 28 postmenopausal women aged 55–75 were recruited in a double-blinded parallel study, subjects consumed two capsules, containing 500 mg of dry AG whole-root powder, every day for 4 months. Before and after the supplementation regimen each subject performed 30 minutes of treadmill walking on a 5% grade incline at an estimated 60% of VO2max. These data results suggest that chronic AG supplementation at the given dose can cause an oxidative stress in postmenopausal women, as reflected by the elevated oxidative damage markers and the increased erythrocyte antioxidant enzyme activity [23]. 39 participants with type 2 diabetes (6.5 > A1c < 8.4%) placebo-controlled, crossover trial with each intervention lasting 12-weeks. Medications, diet and lifestyle were kept constant. Interventions consisted of 6 g of fiber from KGB together with 3 g of dry AG whole-root powder (KGB and AG) or wheat bran-based, fiber-matched control. Primary endpoint

was the difference in HbA1c levels at week 12. Co-administration of KGB and AG increases the effectiveness of conventional therapy through a moderate but clinically meaningful reduction in HbA1c and lipid concentrations over 12 weeks in patients with type 2 diabetes [164]. AG's various clinical trials have been summarized in "Table 2".

Table 2. *Data from studies deemed low quality or results insignificant were excluded.*

Methods	Administration procedures	Results	Subjects	References
A multisite, double-blind trial randomized	750, 1000, 2000 mg/ 2-times per day, 8-weeks, AG powder extract capsule	Provides support for the use of AG to ameliorate Cancer-Related Fatigue	Human	[21]
A double-blind, randomized, cross-over clinical trial	500 mg/ 6-times per day, 8-weeks, AG powder extract capsule	Added to conventional treatment provided an effective and safe adjunct in the management of T2DM	Human	[20]
A double-blind, placebo-controlled, parallel design	500 mg / 6-times per day, 12-weeks, AG powder capsule	Addition to conventional therapy in T2DM with concomitant hypertension improved arterial stiffness and attenuated systolic BP	Human	[159]
A double-blind, placebo-controlled, balanced, crossover design	100, 200, 400 mg, followed by evaluation of cognitive performance, AG powder extract capsule	benefit working memory and extend the age range of this effect to middle-aged individuals	Human	[160]
40 healthy individuals	(250–1000μg mL^{-1}) at 90 min postirradiation, measured for their total antioxidant capacity (TAC) and the reactive oxygen species (ROS), AG powder extract	A relatively nontoxic natural compound that holds radioprotective potential in human lymphocytes even when applied at 90 minutes postirradiation.	[human]	[158]

6. Toxicity/Adverse Effects

Ongoing studies have demonstrated that through the numerous unregulated cultivated procedures that AG is grown, fungal molds, pesticides, and various metals and residues have contaminated some crops in unregulated settings. Despite the fact that these effects are not considerably substantial, they do pose health concerns that could lead to neurological problems, intoxication, cardiovascular disease and cancer [169]. The noted toxicity of AG in Oriental Medicine states that the inappropriate use of this herb which has been noted to cause such side effects as headache, a feeling of weakness, apathy, feeling of intolerance to cold temperatures, a distended abdomen, vomiting, and delayed menstruation. Allergic reactions have also been reported, including drug rash and asthma [14]. Individuals requiring anticoagulant treatment such as warfarin should avoid use of ginseng, it is additionally not prescribed for individuals with impaired liver or renal function, or amid pregnancy or breastfeeding [166]. Qualities and properties of ginsenosides rely upon on the processing; certain extraction methods can bring about estrogenic properties. Specifically, ginseng derived from methanol extraction, as opposed to water extraction, does exhibit estrogenic properties and has been found to proliferate cancer cells in breast cell lines in vitro [123, 167, 170]. An AG water extract was unitized to investigate the mutagenicity in Salmonella typhimurium strain TM677. At concentrations up to 36 mg AG extract/ml of culture media, there were no mutagenic response detected [168]. A pilot trial with aim to examine whether any of three dose measurements of Wisconsin *Panax quinquefolius* may help cancer-related fatigue. The auxiliary aim was to evaluate toxicity. There seemed, by all accounts, some activity and tolerable toxicity at 1,000–2,000 mg/day doses of AG with regard to cancer-related fatigue. what's more, there were no statistically significant differences by arm for the following self-reported side effects assessed per the symptom experience diary: nausea, dizziness, nervousness, headache, trouble falling asleep, and trouble staying asleep [161]. Another Wisconsin *Panax quinquefolius* clinical trial with regard to cancer-related fatigue also showed the frequency, severity and degree of association between the intervention and reported adverse events were not fundamentally different among each of the three treatment arms. the 8 weeks of treatment. Tolerable toxicity at 1,000–2,000 mg/day doses of AG with regard to cancer-related fatigue scores showed almost no change over the course of the study (no more than 5 points out of 100) for nausea, vomiting, nervousness, anxiety, trouble sleeping, and loose stools. With loose stools at 4 weeks (–0.8) and pain at 8 weeks (–0.3) were the only adverse effects worse than baseline, and it is noted that these occurred only in the placebo group. All other symptoms improved over the course of the study further demonstrating the safety of AG during the course of treatment [21]. To assess the safety and tolerability of AG in children. The clinical trial reported no serious adverse occasions were reported. The frequency, recurrence, seriousness of association between the intervention and reported adverse events were not fundamentally different among each of the three treatment arms [156]. Taking everything into account, the selected AG treatment produced rather convincing long-term clinical safety when administered as an adjunct to conventional antihypertensive and antidiabetic treatment. The present study shows that AG did not change any of the contemplated safety parameters, namely, renal, hepatic, or hemostatic function [165]. A clinical preliminary trial of efficacy and safety of AG extract on glycemic control and cardiovascular risk factors in individuals with type 2 diabetes. The safety parameters included markers of hepatic alanine amino-transferase (ALT) and renal (serum creatinine) function. Adverse events were reported and checked all through the preliminary trial. There was no distinction in hepatic or renal function parameters found within and between treatments. AG extract added to conventional therapy provided an effective and safe adjunct in the management of T2DM [20].

7. Conclusion

The main bioactive components of AG are previously researched extensively, the chemical analysis data exhibited that ginseng ginsenosides or triterpenoid saponins possess diversity in their structures. Ginsenosides can likewise be changed to other compounds by heat processing treatment. Since most AG studies focus on the chemical and molecular analysis of the ginseng root or the root extract concentrate but do not discuss of clinical effects, discussion of chemical and molecular analysis of AG is beyond the scope of this article. Various pharmacological actions of AG have been observed in past studies on the central nervous, cardiovascular, endocrine, and immune systems. AG neuroprotective, cardioprotective, antidiabetic, antioxidant and anticancer properties have been reviewed above. There are numerous published clinical investigations utilizing AG on cardiovascular disease, diabetes, central nervous, immune systems and fatigue. Taking everything into account, among the tonic herbs on the Oriental Medicine market, AG is widely studied also by appropriate clinical trials highlighting the beneficial effects compared to a low number of potential toxic effects, thus further scientific evidence based studies are needed to create novel drug and therapy treatments of important pathologies. In conclusion, we must know more to answer the inquiries regarding the observed effects of AG in complementary and integrated medicine. In the future, far reaching enthusiasm for AG seems certain to ensure continued research with this herb. With the pattern of interdisciplinary research and the development of modern combinatorial techniques, the likelihood of gaining novel agents and adjunct therapy in treating important diseases along with supplementing conventional treatment from AG appears to be encouraging.

References

[1] International Affairs U.S. fish & Wildlife Service, www.fws.gov/international/plants/american-ginseng.html

[2] University of Wisconsin, http://corn.agronomy.wisc.edu/Crops/Ginseng.aspx

[3] Peake BM, Tong AY, Wells WJ, Harraway JA, Niven BE, Weege B, et al. “Determination of trace metal concentrations in ginseng (*Panax Quinquefolius* (American)) roots for forensic comparison using Inductively Coupled Plasma Mass-Spectrometry,” *Forensic Sci Int*. 2015 Jun; 251: 214-219. doi: 10.1016/j.forsciint.2015.03.011. Epub 2015 Mar 24.

[4] Kiangsu Institute of Modern Medicine. Encyclopedia of Chinese Drug. Shanghai: *Shanghai Scientific Technical Publication*; 1977. p 29–36, 850–851. [In Chinese]

[5] Zhang LX. “A preliminary study on the history of American Ginseng cultivation in the United States,” [J] *Special Wild Economic Animal and Plant Research,* 1987 (4): 23-25. [In Chinese]

[6] Stone JA.”The status of acupuncture and oriental medicine in the United States,” *Chin J Integr Med*. 2014 Apr; 20 (4): 243-249. doi: 10.1007/s11655-014-1776-0. Epub 2014 Apr 3.

[7] Harkey MR, Henderson GL, Gershwin ME, Stern JS, Hackman RM. Variability in commercial ginseng products: an analysis of 25 preparations. Am J Clin Nutr. 2001; 73: 1101–1106.

[8] Editor Board of Zhong Hua Ben Cao. The Chinese Herbal (Zhong Hua Ben Cao). *Shanghai Science and Technology Press*; Shanghai: 1999.

[9] Vuksan V, Sievenpiper JL, Koo VY, 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): 1009-1013.

[10] Röhrig B, du Prel JB, Wachtlin D, Blettner M. “Types of study in medical research: part 3 of a series on evaluation of scientific publications,” *Dtsch Arztebl Int*. 2009 Apr; 106 (15): 262–268.

[11] Hoffman D. Medical herbalism: the science and practice of herbal medicine. Rochester, VT: *Healing Arts Press*, 2003: 570–582.

[12] Attele AS, Wu JA, Yuan CS. “Ginseng pharmacology: multiple constituents and multiple actions,” *Biochem Pharmacol*. 1999; 58: 1685–1693.

[13] Yuan CS, Wang CZ, Wicks SM, Qi LW. ”Chemical and pharmacological studies of saponins with a focus on American ginseng,” *J Ginseng Res*. 2010 Sep 1; 34 (3): 160-7.

[14] Bensky, Dan (2004) Chinese Herbal Medicine Materia Medica. *Eastland Press*, third edition.

[15] II. Brekhman and IV. Dardymov, “New substances of plant origin which increase nonspecific resistance,” *Annual Review of Pharmacology*, vol. 9, pp. 419–430, 1969.

[16] Radad K, Gille G, Liu L, Rausch WD. “Use of ginseng in medicine with emphasis on neurodegenerative disorders,” *J Pharmacol Sci*. 2006; 100: 175–186.

[17] Mancuso C, Santangelo R. “*Panax* ginseng and *Panax quinquefolius*: From pharmacology to toxicology,” *Food Chem Toxicol*. 2017 Sep; 107 (Pt A): 362-372. doi: 10.1016/j.fct.2017.07.019. Epub 2017 Jul 8.

[18] Chen CF, Chiou WF, Zhang JT. "Comparison of the pharmacological effects of *Panax* ginseng and *Panax quinquefolium*," *Acta Pharmacol Sin*. 2008 Sep; 29 (9): 1103-8. doi: 10.1111/j.1745-7254.2008.00868.x.

[19] Wang Y, Choi HK, Brinckmann JA, Jiang X, Huang L. “Chemical analysis of Panax quinquefolius (North American ginseng): A review,” *J Chromatogr A*. 2015 Dec 24; 1426: 1-15. doi: 10.1016/j.chroma.2015.11.012. Epub 2015 Nov 14.

[20] Vuksan V, Xu ZZ, Jovanovski E, Jenkins AL, Beljan-Zdravkovic U, Sievenpiper JL, Mark Stavro P, Zurbau A, Duvnjak L, Li MZC."Efficacy and safety of American ginseng (*Panax quinquefolius L*.) extract on glycemic control and cardiovascular risk factors in individuals with type 2 diabetes: a double-blind, randomized, cross-over clinical trial," *Eur J Nutr*. 2018 Feb 24. doi: 10.1007/s00394-018-1642-0.

[21] Barton DL, Liu H, Dakhil SR, Linquist B, Sloan JA, Nichols CR, McGinn TW, Stella PJ, Seeger GR, Sood A, Loprinzi CL. "Wisconsin Ginseng (*Panax quinquefolius*) to Improve Cancer-Related Fatigue: A Randomized, Double-Blind Trial, N07C2," *J Natl Cancer Inst*. 2013 Aug 21; 105 (16): 1230-8. doi: 10.1093/jnci/djt181. Epub 2013 Jul 13.

[22] Scholey A, Ossoukhova A, Owen L, Ibarra A, Pipingas A, He K, Roller M, Stough C. "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. doi: 10.1007/s00213-010-1964-y. Epub 2010 Jul 31.

[23] Dickman JR, Koenig RT, Ji LL. "American Ginseng Supplementation Induces an Oxidative Stress in Postmenopausal Women," *J Am Coll Nutr*. 2009 Apr; 28 (2): 219-28.

[24] Zhao HZ, editor. "Cyclopedia of *Panax* ginseng and American ginseng," Hong Kong: *Rong-Zhai Publishers*; 1998. p 9. [In Chinese]

[25] Li FY, editor. *Panax* ginseng and American ginseng. Beijing: *Chinese Agriculture Scientech Press*; 2006. p. 587–91. [In Chinese]

[26] Tanaka O, Sakai R. "Saponins of Ginseng and related plants. In: Herz W, Grisebach H (Editors). Progress in chemistry of organic natural products," Vienna: *Spring-Verlag*, 1984. p 1–76.

[27] Yang CR, Zhou J, Tanaka O. "Chemotaxanomic studies and the utilization of *Panax* species," *Acta Bot Yunnanica* 1988 Suppl. 1: 47–62. [In Chinese]

[28] Li FY, editor. "*Panax* ginseng and American ginseng," Beijing: *Chinese Agriculture Scientech Press*; 2006. p 486–7. [In Chinese]

[29] Kim, J. S., Kim, Y., Han, S. H., Jeon, J. Y., Hwang, M., Im, Y. J., Kim, J. H., Lee, S. Y., Chae, S. W., Kim, M. G., 2013a. "Development and validation of an LC-MS/MS method for determination of compound K in human plasma and clinical application," *J. Ginseng Res*. 37, 135e141.

[30] Qu CL, Bai YP, Jin XQ, Wang YT, Zhang K, You JY, Zhang HQ. "Study on ginsenosides in different parts and ages of *Panax quinquefolius L*," *Food Chem. 2009*; 115: 340–346.

[31] Reeds DN, Patterson BW, "Okunade A, et al. Ginseng and ginsenoside Re do not improve beta-cell function or insulin sensitivity in overweight and obese subjects with impaired glucose tolerance or diabetes," *Diabetes Care*. 2011; 34: 1071–1076.

[32] Huang GD, Zhong XF, Deng ZY, Zeng R. "Proteomic analysis of ginsenoside Re attenuates hydrogen peroxide-induced oxidative stress in human umbilical vein endothelial cells," *Food Funct*. 2016 May 18; 7 (5): 2451-61. doi: 10.1039/c6fo00123h. Epub 2016 May 10.

[33] Court WA, Reynolds LB, Hendel JG. "Influence of root age on the concentration of ginsenosides of American ginseng (*Panax quinquefolium*)," *Can J Plant Sci* 1996; 76: 853–5.

[34] Wills RBH, Du XW, "Stuart DI. Changes in ginsenosides in Australian-grown American ginseng plants (*Panax quinquefolium L.*)," *Aust J Exp Agric* 2002; 42: 1119–23.

[35] Li WK, Gu CG, Zhang HJ, Awang DVC, Fitzloff JF, Fong HHS, et al. "Use of high-performance liquid chromatography-tandem mass spectrometry to distinguish *Panax* ginseng L. A. Meyer (Asian ginseng) and *Panax quinquefolium L*. (North American ginseng)," *Anal Chem 2000*; 72: 5417–22.

[36] Sun K, Wang CS, Guo J, Horie Y, Fang SP, Wang F, et al. "Protective effects of ginsenoside Rb1, ginsenoside Rg1, and notoginsenoside R1 on lipopolysaccharide-induced microcirculatory disturbance in rat mesentery," Life Sci 2007; 81: 509–18.

[37] Wu CF, Bi XL, Yang JY, Zhan JY, Dong YX, Wang JH, et al. "Differential effects of ginsenosides on NO and TNF-alpha production by LPS-activated N9 microglia," *Intern Immnuopharmacol* 2007; 7: 312–20.

[38] Liu ZX, Liu XC. "Effect of ginsenoside Rb1 and Re on cardiomyocyte apoptosis after ischemia and reperfusion in rats," *Chin J Histochem Cytochem* 2002; 11: 374–7. [In Chinese]

[39] Ro JY, Ahn YS, Kim KH. "Inhibitory effect of ginsenoside on the mediator release in the guinea pig lung mast cells activated by specific antigen-antibody reactions," *Int J Immunopharmacol* 1998; 20: 625–41.

[40] Keum YS, Han SS, Chun KS, Park KK, Park JH, Lee SK et al. "Inhibitory effects of the ginsenoside Rg3 on phorbol ester-induced cyclooxygenase-2 expression, NF-kappaB activation and tumor promotion," *Mutat Res* 2003; 523–524: 75–8.

[41] Park EK, Shin YW, Lee HU, Kim SS, Lee YC, Lee BY, et al. "Inhibitory effect of ginsenoside Rb1 and compound K on NO and prostaglandin E2 biosynthesis of RAW 264.7 cells induced by lipopolysaccharide," *Biol Pharm Bull* 2005; 28: 652–6.

[42] Lee TK, Wang W, O'Brien KF, Johnke RM, Wang T, Allison RR, Diaz AL. "Effect of North American ginseng on 137Cs-induced micronuclei in human lymphocytes: a comparison with WR-1065," *Phytother Res.* 2008 Dec; 22 (12): 1614-22. doi: 10.1002/ptr.2533.

[43] Miller SC, Ti L, Shan JJ. "The sustained influence of short term exposure to a proprietary extract of North American ginseng on the hemopoietic cells of the bone marrow, spleen and blood of adult and juvenile mice," *Phytother Res*. 2012 May; 26 (5): 675-81. doi: 10.1002/ptr.3626. Epub 2011 Oct 13.

[44] Miller SC, Ti L, Shan J. "Dietary supplementation with an extract of North American ginseng in adult and juvenile mice increases natural killer cells," *Immunol Invest*. 2012; 41 (2): 157-70. doi: 10.3109/08820139.2011.599087. Epub 2011 Aug 4.

[45] Yan J, Ma Y, Zhao F, Gu W, Jiao Y. 'Identification of immunomodulatory signatures induced by american ginseng in murine immune cells," *Evid Based Complement Alternat Med*. 2013; 2013: 972814. doi: 10.1155/2013/972814. Epub 2013 Nov 11.

[46] Samimi R, Xu WZ, Lui EM, Charpentier PA. "Isolation and immunosuppressive effects of 6″-O-acetylginsenoside Rb1 extracted from North American ginseng," *Planta Med*. 2014 Apr; 80 (6): 509-16. doi: 10.1055/s-0034-1368319. Epub 2014 Mar 31.

[47] Azike CG, Charpentier PA, Lui EM. "Stimulation and suppression of innate immune function by American ginseng polysaccharides: biological relevance and identification of bioactives," *Pharm Res*. 2015 Mar; 32 (3): 876-97. doi: 10.1007/s11095-014-1503-3. Epub 2014 Sep 11.

[48] Chen, J., Wang, Q., Wu, H., Liu, K., Wu, Y., Chang, Y., Wei, W., 2016a. "The ginsenoside metabolite compound K exerts its anti-inflammatory activity by down- regulating memory B cell in adjuvant-induced arthritis," *Pharm. Biol.* 54, 1280e1288.

[49] Qi B, Wang S, Wang Q, Zhang H, Bai XY, He HN, Sun WJ, Liu L, Zhao DQ. "Characterization and immunostimulating effects on murine peritoneal macrophages of a novel protein isolated from *Panax quinquefolius L*," *J Ethnopharmacol*. 2016 Dec 4; 193: 700-705. doi: 10.1016/j.jep.2016.10.034. Epub 2016 Oct 11.

[50] Christensen LP. "Ginsenosides chemistry, biosynthesis, analysis, and potential health effects," *Adv Food Nutr Res*. 2009; 55: 1–99. [PubMed: 18772102]

[51] Nah SY, Kim DH, Rhim H. "Ginsenosides: are any of them candidates for drugs acting on the central nervous system?," *CNS Drug* Rev 2007; 13: 381–404. [PubMed: 18078425]

[52] Quirke V, Gaudilliere J-P. "The Era of Biomedicine: Science, Medicine, and Public Health in Britain and France after the Second World War," *Journal ListMed* Histv. 52 (4); 2008 OctPMC2570449

[53] Chang Y, Huang WJ, Tien LT, Wang SJ. "Ginsenosides Rg1 and Rb1 enhance glutamate release through activation of protein kinase A in rat cerebrocortical nerve terminals (synaptosomes)," *Eur J Pharmacol* 2008; 578: 28–36. [PubMed: 17949708]

[54] Tian J, Fu F, Geng M, Jiang Y, Yang J, Jiang W, Wang C, Liu K. "Neuroprotective effect of 20(S)- ginsenoside Rg3 on cerebral ischemia in rats," *Neurosci Lett* 2005; 374: 92–97. [PubMed: 15644271]

[55] Benishin CG, Lee R, Wang LC, Liu HJ. "Effects of ginsenoside Rb1 on central cholinergic metabolism," *Pharmacology* 1991; 42: 223–229. [PubMed: 1852782]

[56] Lee JH, Jeong SM, Kim JH, Lee BH, Yoon IS, Choi SH, Lee SM, Park YS, Kim SS, Kim HC, Lee BY, Nah SY. "Effects of ginsenosides and their metabolites on voltage-dependent Ca(2+) channel subtypes," *Mol Cells* 2006; 21: 52–62. [PubMed: 16511347]

[57] Mook-Jung I, Hong HS, Boo JH, Lee KH, Yun SH, Cheong MY, Joo I, Huh K, Jung MW. "Ginsenoside Rb1 and Rg1 improve spatial learning and increase hippocampal synaptophysin level in mice," *J Neurosci Res* 2001; 63: 509–515. [PubMed: 11241586]

[58] Yuan QL, Yang CX, Xu P, Gao XQ, Deng L, Chen P, Sun ZL, Chen QY. "Neuroprotective effects of ginsenoside Rb1 on transient cerebral ischemia in rats," *Brain Res* 2007; 1167: 1–12. [PubMed: 17663984]

[59] Chen X, Huang T, Zhang J, Song J, Chen L, Zhu Y. "Involvement of calpain and p25 of CDK5 pathway in ginsenoside Rb1's attenuation of beta-amyloid peptide25-35-induced tau hyperphosphorylation in cortical neurons," *Brain Res* 2008; 1200: 99–106. [PubMed: 18289510]

[60] Xue JF, Liu ZJ, Hu JF, Chen H, Zhang JT, Chen NH. "Ginsenoside Rb1 promotes neurotransmitter release by modulating phosphorylation of synapsins through a cAMP-dependent protein kinase pathway," *Brain Res* 2006; 1106: 91–98. [PubMed: 16836988]

[61] Zhao H, Li Q, Pei X, Zhang Z, Yang R, Wang J, Li Y. "Long-term ginsenoside administration prevents memory impairment in aged C57BL/6J mice by up-regulating the synaptic plasticity-related proteins in hippocampus," *Behav Brain Res* 2009; 201: 311–317. [PubMed: 19428650]

[62] Zhao H, Li Q, Zhang Z, Pei X, Wang J, Li Y. "Long-term ginsenoside consumption prevents memory loss in aged SAMP8 mice by decreasing oxidative stress and up-regulating the plasticity- related proteins in hippocampus," *Brain Res* 2009; 1256: 111–122. [PubMed: 19133247]

[63] Rasheed, N., Tyagi, E., Ahmad, A., Siripurapu, K. B., Lahiri, S., Shukla, R., Palit, G., 2008. "Involvement of monoamines and proinflammatory cytokines in mediating the anti-stress effects of Panax quinquefolium," *J. Ethnopharmacol*. 117, 257e262.

[64] Hu SQ, Yu HM, Liu TS, Yang DJ, Chen XZ, He CJ. "[Neuroprotective effects of water extracts of American Ginseng on SH-SY5Y cells apoptosis induced by Abeta25-35]," *Zhong Yao Cai*. 2008 Sep; 31 (9): 1373-7

[65] Xu BB, Liu CQ, Gao X, Zhang WQ, Wang SW, Cao YL. "Possible mechanisms of the protection of ginsenoside Re against MPTP-induced apoptosis in substantia nigra neurons of Parkinson's disease mouse model," *J Asian Nat Prod Res*. 2005; 7: 215–224. [PubMed: 15621629]

[66] Xu L, Chen WF, Wong MS. "Ginsenoside Rg1 protects dopaminergic neurons in a rat model of Parkinson's disease through the IGF-I receptor signalling pathway," *Br J Pharmacol*. 2009; 158: 738–748. [PubMed: 19703168]

[67] Bao HY, Zhang J, Yeo SJ, Myung CS, Kim HM, Kim JM, Park JH, Cho J, Kang JS. "Memory enhancing and neuroprotective effects of selected ginsenosides," *Arch Pharm Res*. 2005; 28: 335– 342. [PubMed: 15832823]

[68] Wang YZ, Chen J, Chu SF, Wang YS, Wang XY, Chen NH, Zhang JT. "Improvement of memory in mice and increase of hippocampal excitability in rats by ginsenoside Rg1's metabolites ginsenoside Rh1 and protopanaxatriol," *J Pharmacol Sci*. 2009b; 109: 504–510. [PubMed: 19372633]

[69] Zhang GZ, Liu AL, Zhou YB, San X, Jin TW, Jin Y. "Panax ginseng ginsenoside-Rg(2) protects memory impairment via anti-apoptosis in a rat model with vascular dementia," *J Ethnopharmacol*. 2008; 115: 441–448. [PubMed: 18083315]

[70] Zhao WJ, Li PY. "Ginsenoside Re improved memory impairment in aged rats and mice," *Neurobiol Aging*. 2004; 25: S582–S583.

[71] Bowie LE1, Roscoe WA, Lui EM, Smith R, Karlik SJ. "Effects of an aqueous extract of North American ginseng on MOG(35-55)-induced EAE in mice," *Can J Physiol Pharmacol*. 2012 Jul; 90 (7): 933-9. doi: 10.1139/y2012-092. Epub 2012 Jun 21.

[72] Wang JY, Yang JY, Wang F, Fu SY, Hou Y, Jiang B, Ma J, Song C, Wu CF. "Neuroprotective effect of pseudoginsenoside-f11 on a rat model of Parkinson's disease induced by 6-hydroxydopamine," *Evid Based Complement Alternat Med*. 2013; 2013: 152798. doi: 10.1155/2013/152798. Epub 2013 Dec 10.

[73] 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. doi: 10.1007/s00210-013-0925-5. Epub 2013 Oct 17.

[74] Shin, K., Guo, H., Cha, Y., Ban, Y. H., Seo da, W., Choi, Y., Kim, T. S., Lee, S. P., Kim, J. C., Choi, E. K., Yon, J. M., Kim, Y. B., 2016. "CereboostTM, an American ginseng extract, improves cognitive function via up-regulation of choline acetyltransferase expression and neuroprotection. *Regul Toxicol Pharmacol*. 78, 53e58.

[75] Dou HC, Chen JY, Ran TF, Jiang WM. "*Panax quinquefolius* saponin inhibits endoplasmic reticulum stress-mediated apoptosis and neurite injury and improves functional recovery in a rat spinal cord injury model," *Biomed Pharmacother*. 2018 Jun; 102: 212-220. doi: 10.1016/j.biopha.2018.03.074. Epub 2018 Mar 22.

[76] Shao ZH, Xie JT, Vanden Hoek TL, Mehendale S, Aung H, Li CQ, Qin Y, Schumacker PT, Becker LB, Yuan CS. "Antioxidant effects of American ginseng berry extract in cardiomyocytes exposed to acute oxidant stress," *Biochim Biophys Acta* 2004; 1670: 165–171. [PubMed: 14980443]

[77] Mehendale SR, Wang CZ, Shao ZH, Li CQ, Xie JT, Aung HH, Yuan CS. "Chronic pretreatment with American ginseng berry and its polyphenolic constituents attenuate oxidant stress in cardiomyocytes," *Eur J Pharmacol* 2006; 553: 209–214. [PubMed: 17092497]

[78] Xie JT, Shao ZH, Vanden Hoek TL, Chang WT, Li J, Mehendale S, Wang CZ, Hsu CW, Becker LB, Yin JJ, Yuan CS. "Antioxidant effects of ginsenoside Re in cardiomyocytes," *Eur J Pharmacol* 2006; 532: 201–207. [PubMed: 16497296]

[79] Wang CL, Shi DZ, Yin HJ. "Effect of *panax quinquefolius* saponin on angiogenesis and expressions of VEGF and bFGF in myocardium of rats with acute myocardial infarction," *Zhongguo Zhong Xi Yi Jie He Za Zhi* 2007; 27: 331–334. [PubMed: 17526173]

[80] Prior RL, Cao G. "Analysis of botanicals and dietary supplements for antioxidant capacity: a review," *J AOAC Int* 2000; 83: 950–956. [PubMed: 10995120]

[81] Wang CZ, Mehendale SR, Yuan CS. "Commonly used antioxidant botanicals: active constituents and their potential role in cardiovascular illness," *Am J Chin Med* 2007; 35: 543–558. [PubMed: 17708622]

[82] Li JQ, Ichikawa T, Jin Y, Hofseth LJ, Nagarkatti P, Nagarkatti M, Windust A, Cui TX. "An essential role of Nrf2 in American ginseng-mediated anti-oxidative actions in cardiomyocytes," *J Ethnopharmacol*. 2010b; 130: 222–230. [PubMed: 20447451]

[83] Wu, Y., Lu, X., Xiang, F. L., Lui, E. M., Feng, Q., 2011b. "North American ginseng protects the heart from ischemia and reperfusion injury via upregulation of endothelial nitric oxide synthase," *Pharmacol*. Res. 64, 195e202.

[84] Tsutsumi, Y. M., Tsutsumi, R., Mawatari, K., Nakaya, Y., Kinoshita, M., Tanaka, K., Oshita, S., 2011. "Compound K, a metabolite of ginsenosides, induces cardiac protection mediated nitric oxide via Akt/PI3K pathway," *Life Sci*. 88, 725e729.

[85] Wu Q, Wang W, Li S, Nagarkatti P, Nagarkatti M, Windust A, Wang XL, Tang D, Cui T. "American ginseng inhibits vascular smooth muscle cell proliferation via suppressing Jak/Stat pathway," *J Ethnopharmacol*. 2012 Dec 18; 144 (3): 782-5. doi: 10.1016/j.jep.2012.09.046. Epub 2012 Oct 4.

[86] Jiang M, Murias JM, Chrones T, Sims SM, Lui E, Noble EG. "American ginseng acutely regulates contractile function of rat heart," *Front Pharmacol*. 2014 Mar 14; 5: 43. doi: 10.3389/fphar.2014.00043. eCollection 2014.

[87] Qu C, Li B, Lai Y, Li H, Windust A, Hofseth LJ, Nagarkatti M, Nagarkatti P, Wang XL, Tang D, Janicki JS, Tian X, Cui T. "Identifying panaxynol, a natural activator of nuclear factor erythroid-2 related factor 2 (Nrf2) from American ginseng as a suppressor of inflamed macrophage-induced cardiomyocyte hypertrophy," *J Ethnopharmacol*. 2015 Jun 20; 168: 326-36. doi: 10.1016/j.jep.2015.04.004. Epub 2015 Apr 14.

[88] Wu Y, Qin C, Lu X, Marchiori J, Feng Q. "North American ginseng inhibits myocardial NOX2-ERK1/2 signaling and tumor necrosis factor-α expression in endotoxemia," *Pharmacol Res*. 2016 Sep; 111: 217-225. doi: 10.1016/j.phrs.2016.06.010. Epub 2016 Jun 16.

[89] Tang X, Gan XT, Rajapurohitam V, Huang CX, Xue J, Lui EM, Karmazyn M. "North American ginseng (*Panax quinquefolius*) suppresses β-adrenergic-dependent signalling, hypertrophy, and cardiac dysfunction," *Can J Physiol Pharmacol. 2016 Dec; 94 (12): 1325-1335. Epub 2016 Aug 17.*

[90] Blumenthal M. The ABC clinical guide to herbs. New York, NY: Theime, 2003: 211–225.

[91] Sen S, Querques MA, Chakrabarti S. "North American ginseng (*Panax quinquefolius*) prevents hyperglycemia and associated pancreatic abnormalities in diabetes," *J Med Food*. 2013; 16: 587–592 l.

[92] Xie JT, Mehendale SR, Wang A, et al. "American ginseng leaf: ginsenoside analysis and hypoglycemic activity," *Pharmacol Res*. 2004; 49: 113–117.

[93] Kimura M, Waki I, Chujo T, et al. "Effects of hypoglycemic components in ginseng radix on blood insulin level in alloxan diabetic mice and on insulin release from perfused rat pancreas," *J Pharmaco Bio Dyn*. 1981; 4: 410–417.

[94] Xie JT, Mehendale S, Yuan CS. "Ginseng and diabetes," *Am J Chin Med*. 2005; 33: 397–404.

[95] Sen S, Chen S, Feng B, Yuexiu W, Lui EK, Chakrabarti S. "Preventive effects of North American ginseng (*Panax quinquefolius*) on diabetic retinopathy and cardiomyopathy," Phytother Res. 2012; 27: 290–298.

[96] Sen S, Chen S, Feng B, Yuexiu W, Lui EM, Chakrabarti S. "Preventive effects of north American ginseng (*Panax quinquefolium*) on diabetic nephropathy," Phytomedicine. 2012; 19: 494–505.

[97] Chakrabarti S, Sen S, Lui E. "Effect of ginseng therapy on diabetes and its chronic complications: lessons learned," *J Complement Integr Med*. 2017 May 11; 14 (4). pii: /j/jcim.2017.14.issue-4/jcim-2016-0166/jcim-2016-0166.xml. doi: 10.1515/jcim-2016-0166.

[98] Qi LW, Liu EH, Chu C, Peng YB, Cai HX, Li P. "Anti-Diabetic Agents from natural products-An update from 2004 to 2009," *Curr Top Med Chem*. 2010a; 10: 434–457. [PubMed: 20180758]

[99] Dey L, Xie JT, Wang A, Wu J, Maleckar SA, Yuan CS. "Anti-hyperglycemic effects of ginseng: comparison between root and berry," *Phytomedicine* 2003; 10: 600–605. [PubMed: 13678250]

[100] Shang W, Yang Y, Jiang B, Jin H, Zhou L, Liu S, Chen M. "Ginsenoside Rb1 promotes adipogenesis in 3T3-L1 cells by enhancing PPARgamma2 and C/EBPalpha gene expression," *Life Sci* 2007; 80: 618–625. [PubMed: 17129589]

[101] Shang W, Yang Y, Zhou L, Jiang B, Jin H, Chen M. "Ginsenoside Rb1 stimulates glucose uptake through insulin-like signaling pathway in 3T3-L1 adipocytes," *J Endocrinol*. 2008; 198: 561–569. [PubMed: 18550785]

[102] Xie JT, Mehendale SR, Li X, Quigg R, Wang X, Wang CZ, Wu JA, Aung HH, PAR, Bell GI, Yuan CS. "Anti-diabetic effect of ginsenoside Re in ob/ob mice," *Biochim Biophys Acta*. 2005b; 1740: 319–325. [PubMed: 15949698]

[103] Yokozawa T, Yasui T, Oura H. "Stimulation of rna-polymerase activity by ginsenoside-Rb2 in diabeticrats," *Phytother Res*. 1993; 7: 240–243.

[104] Lee WK, Kao ST, Liu IM, Cheng JT. "Increase of insulin secretion by ginsenoside Rh2 to lower plasma glucose in wistar rats," *Clin Exp Pharmacol Physiol*. 2006; 33: 27–32. [PubMed: 16445695]

[105] Yoon SH, Han EJ, Sung JH, Chung SH. "Anti-diabetic effects of compound K versus metformin versus compound K-metformin combination therapy in diabetic db/db mice," *Biol Pharm Bull*. 2007; 30: 2196–2200. [PubMed: 17978500]

[106] Han KL, Jung MH, Sohn JH, Hwang JK. "Ginsenoside 20(S)-protopanaxatriol (PPT) activates peroxisome proliferator-activated receptor gamma (PPAR gamma) in 3T3-L1 adipocytes," *Biol Pharm Bull*. 2006; 29: 110–113. [PubMed: 16394521]

[107] Lin E, Wang Y, Mehendale S, Wang CZ, Xie JT, Aung H, Yuan CS. "Antioxidant protection by American ginseng in pancreatic beta-cells," *Faseb J*. 2005; 19: A97–A97.

[108] Lin E, Wang Y, Mehendale S, Sun S, Wang CZ, Xie JT, Aung HH, Yuan CS. "Antioxidant protection by American ginseng in pancreatic beta-cells," *Am J Chinese Med*. 2008; 36: 981–988.

[109] Park S, Ahn IS, Kwon DY, Ko BS, Jun WK. "Ginsenosides Rb1 and Rg1 suppress triglyceride accumulation in 3T3-L1 adipocytes and enhance beta-cell insulin secretion and viability in Min6 cells via PKA-dependent pathways," *Biosci Biotechnol Biochem*. 2008; 72: 2815–2823. [PubMed: 18997435]

[110] Kim HY, Kang KS, Yamabe N, Nagai R, Yokozawa T. "Protective effect of heat-processed American ginseng against diabetic renal damage in rats," *J Agr Food Chem*. 2007a; 55: 8491–8497. [PubMed: 17894462]

[111] Stohs SJ. "The role of free radicals in toxicity and disease," *J Basic Clin Physiol Pharmacol* 1995; 6: 205–228. [PubMed: 8852268]

[112] Cetin A, Kaynar L, Kocyigit I, Hacioglu SK, Saraymen R, Ozturk A, Sari I, Sagdic O. "Role of grape seed extract on methotrexate induced oxidative stress in rat liver," *Am J Chin Med* 2008; 36: 861–872. [PubMed: 19051353]

[113] Xie JT, Wang CZ, Li XL, Ni M, Fishbein A, Yuan CS. "Anti-diabetic effect of American ginseng may not be linked to antioxidant activity: comparison between American ginseng and Scutellaria baicalensis using an ob/ob mice model," Fitoterapia 2009; 80: 306–311. [PubMed: 19358881]

[114] Shen, L., Haas, M., Wang, D. Q., May, A., Lo, C. C., Obici, S., Tso, P., Woods, S. C., Liu, M., 2015. "Ginsenoside Rb1 increases insulin sensitivity by activating AMP-activated protein kinase in male rats," *Physiol*. Rep. 3, e12543.

[115] Corbit R, Ebbs S, King ML, Murphy LL. "The influence of lead and arsenite on the inhibition of human breast cancer MCF-7 cell proliferation by American ginseng root (*Panax quinquefolius L.*)," Life Sci 2006; 78: 1336–1340. [PubMed: 16288926]

[116] Duda RB, Zhong Y, Navas V, Li MZ, Toy BR, Alavarez JG. "American ginseng and breast cancer therapeutic agents synergistically inhibit MCF-7 breast cancer cell growth," *J Surg Oncol* 1999; 72: 230–239. [PubMed: 10589039]

[117] Wang CZ, Aung HH, Ni M, Wu JA, Tong R, Wicks S, He TC, Yuan CS. "Red American ginseng: ginsenoside constituents and antiproliferative activities of heat-processed Panax quinquefolius roots," *Planta Med* 2007; 73: 669–674. [PubMed: 17538869]

[118] Wang CZ, Zhang B, Song WX, Wang A, Ni M, Luo X, Aung HH, Xie JT, Tong R, He TC, Yuan CS. "Steamed American ginseng berry: ginsenoside analyses and anticancer activities," *J Agric Food Chem* 2006; 54: 9936–9942. [PubMed: 17177524]

[119] Xie JT, Wang CZ, Zhang B, Mehendale SR, Li XL, Sun S, Han AH, Du W, He TC, Yuan CS. "*In vitro* and *in vivo* anticancer effects of American ginseng berry: exploring representative compounds," *Biol Pharm Bull* 2009; 32: 1552–1558. [PubMed: 19721231]

[120] Yue PY, Wong DY, Wu PK, Leung PY, Mak NK, Yeung HW, Liu L, Cai Z, Jiang ZH, Fan TP, Wong RN. "The angiosuppressive effects of 20(R)- ginsenoside Rg3," *Biochem Pharmacol* 2006; 72: 437–445. [PubMed: 16793023]

[121] Kim SY, Kim DH, Han SJ, Hyun JW, Kim HS. "Repression of matrix metalloproteinase gene expression by ginsenoside Rh2 in human astroglioma cells," *Biochem Pharmacol* 2007; 74: 1642– 1651. [PubMed: 17880928]

[122] Kim SM, Lee SY, Cho JS, Son SM, Choi SS, Yun YP, Yoo HS, Yoon do Y, Oh KW, Han SB, Hong JT. "Combination of ginsenoside Rg3 with docetaxel enhances the susceptibility of prostate cancer cells via inhibition of NF-kappaB," *Eur J Pharmacol* 2010; 631: 1–9. [PubMed: 20056115]

[123] Duda RB, Kang SS, Archer SY, Meng S, Hodin RA. "American ginseng transcriptionally activates p21 mRNA in breast cancer cell lines," *J Korean Med Sci* 2001; 16 (Suppl): S54–60. [PubMed: 11748377]

[124] Park JA, Lee KY, Oh YJ, Kim KW, Lee SK. "Activation of caspase-3 protease via a Bcl-2- insensitive pathway during the process of ginsenoside Rh2-induced apoptosis," *Cancer Lett* 1997; 121: 73–81. [PubMed: 9459177]

[125] Jia WW, Bu X, Philips D, Yan H, Liu G, Chen X, Bush JA, Li G. "Rh2, a compound extracted from ginseng, hypersensitizes multidrug-resistant tumor cells to chemotherapy," *Can J Physiol Pharmacol* 2004; 82: 431–437. [PubMed: 15389289]

[126] Luo X, Wang CZ, Chen J, Song WX, Luo J, Tang N, He BC, Kang Q, Wang Y, Du W, He TC, Yuan CS. "Characterization of gene expression regulated by American ginseng and ginsenoside Rg3 in human colorectal cancer cells," *Int J Oncol* 2008; 32: 975–983. [PubMed: 18425323]

[127] Aung HH, Mehendale SR, Wang CZ, Xie JT, McEntee E, Yuan CS. "Cisplatin's tumoricidal effect on human breast carcinoma MCF-7 cells was not attenuated by American ginseng," *Cancer Chemother Pharmacol* 2007; 59: 369–374. [PubMed: 16799811]

[128] Mehendale S, Aung H, Wang A, Yin JJ, Wang CZ, Xie JT, Yuan CS. "American ginseng berry extract and ginsenoside Re attenuate cisplatin-induced kaolin intake in rats," *Cancer Chemother Pharmacol* 2005; 56: 63–69. [PubMed: 15791456]

[129] Qi LW, Wang CZ, Yuan CS. "American ginseng: Potential structure-function relationship in cancer chemoprevention," *Biochem Pharmacol*. 2010b; 80: 947–954. [PubMed: 20599804]

[130] Wang CZ, Li XL, Wang QF, Mehendale SR, Fishbein AB, Han AH, Sun S, Yuan CS. "The mitochondrial pathway is involved in American ginseng-induced apoptosis of SW-480 colon cancer cells," Oncol Rep. 2009a; 21: 577–584. [PubMed: 19212614]

[131] Li XL, Wang CZ, Sun S, Mehendale SR, Du W, He TC, Yuan CS. "American ginseng berry enhances chemopreventive effect of 5-FU on human colorectal cancer cells," *Oncol Rep*. 2009d; 22: 943–952. [PubMed: 19724877]

[132] Pawar AA, Tripathi DN, Ramarao P, Jena G. "Protective effects of American ginseng (*Panax quinquefolium*) against mitomycin C induced micronuclei in mice," *Phytother Res*. 2007; 21: 1221–1227. [PubMed: 17661327]

[133] Sun S, Qi LW, Du GJ, Mehendale SR, Wang CZ, Yuan CS. "Red notoginseng: higher ginsenoside content and stronger anticancer potential than Asian and American ginseng," *Food Chem*. 2011; 125: 1299–1305. [PubMed: 21344064]

[134] Sengupta S, Toh SA, Sellers LA, Skepper JN, Koolwijk P, Leung HW, Yeung HW, Wong RNS, Sasisekharan R, Fan TPD. "Modulating angiogenesis - The yin and the yang in ginseng," *Circulation*. 2004; 110: 1219–1225. [PubMed: 15337705]

[135] Jin Y, Kotakadi VS, Ying L, Hofseth AB, Cui XL, Wood PA, Windust A, Matesic LE, Pena EA, Chiuzan C, Singh NP, Nagarkatti M, Nagarkatti PS, Wargovich MJ, Hofseth LJ. "American ginseng suppresses inflammation and DNA damage associated with mouse colitis," *Carcinogenesis*. 2008; 29: 2351–2359. [PubMed: 18802031]

[136] Jin Y, Hofseth AB, Cui XL, Windust AJ, Poudyal D, Chumanevich AA, Matesic LE, Singh NP, Nagarkatti M, Nagarkatti PS, Hofseth LJ. "American ginseng suppresses colitis through p53-mediated apoptosis of inflammatory cells," *Cancer Prev Res*. 2010; 3: 339–347.

[137] King ML, Murphy LL. "Role of cyclin inhibitor protein p21 in the inhibition of HCT116 human colon cancer cell proliferation by American ginseng (*Panax quinquefolius*) and its constituents. Phytomedicine," 2010; 17: 261–268. [PubMed: 19674880]

[138] Lee SJ, Ko WG, Kim JH, Sung JH, Lee SJ, Moon CK, Lee BH. "Induction of apoptosis by a novel intestinal metabolite of ginseng saponin via cytochrome c-mediated activation of caspase-3 protease," *Biochem Pharmacol*. 2000; 60: 677–685. [PubMed: 10927026]

[139] Peralta EA, Murphy LL, Minnis J, Louis S, Dunnington GL. "American ginseng inhibits induced COX-2 and NFKB activation in breast cancer cells," *J Surg Res*. 2009; 157: 261–267. [PubMed: 19815237]

[140] Ichikawa T, Li JQ, Nagarkatti P, Nagarkatti M, Hofseth LJ, Windust A, Cui TX. "American ginseng preferentially suppresses STAT/iNOS signaling in activated macrophages," *J Ethnopharmacol*. 2009; 125: 145–150. [PubMed: 19505555]

[141] Li BH, Wang CZ, He TC, Yuan CS, Du W. "Antioxidants potentiate American ginseng-induced killing of colorectal cancer cells," *Cancer Lett*. 2010a; 289: 62–70. [PubMed: 19716228]

[142] Aggarwal BB, Van Kuiken ME, Iyer LH, Harikumar KB, Sung B. "Molecular Targets of Nutraceuticals Derived from Dietary Spices: Potential Role in Suppression of Inflammation and Tumorigenesis," *Exp Biol Med*. 2009; 234: 825–849.

[143] Cui X, Jin Y, Poudyal D, Chumanevich AA, Davis T, Windust A, Hofseth A, Wu W, Habiger J, Pena E, Wood P, Nagarkatti M, Nagarkatti PS, Hofseth L. "Mechanistic insight into the ability of American ginseng to suppress colon cancer associated with colitis," *Carcinogenesis*. 2010 Oct; 31 (10): 1734-41. doi: 10.1093/carcin/bgq163. Epub 2010 Aug 20.

[144] Poudyal D, Cui X, Mai Le P, Davis T, Hofseth AB, Jin Y, Chumanevich AA, Wargovich MJ, Nagarkatti M, Nagarkatti PS, Windust A, Hofseth LJ. "A limited role of p53 on the ability of a Hexane fraction of American ginseng to suppress mouse colitis," *J Biomed Biotechnol*. 2012; 2012: 785739. doi: 10.1155/2012/785739. Epub 2012 Jul 30.

[145] Poudyal D, Le PM, Davis T, Hofseth AB, Chumanevich A, Chumanevich AA, Wargovich MJ, Nagarkatti M, Nagarkatti PS, Windust A, Hofseth LJ. "A hexane fraction of American ginseng suppresses mouse colitis and associated colon cancer: anti-inflammatory and proapoptotic mechanisms," *Cancer Prev Res (Phila)*. 2012 Apr; 5 (4): 685-96. doi: 10.1158/1940-6207.CAPR-11-0421. Epub 2012 Jan 31.

[146] Chan PC, Huff J. "Hexane fraction of American ginseng suppresses colitis and colon cancer," *Cancer Prev Res (Phila)*. 2012 Jul; 5 (7): 982; author reply 983. doi: 10.1158/1940-6207.CAPR-12-0079. Epub 2012 May 25.

[147] Yu CH, Wang CZ, Yuan CS. "[Progress in anti-cancer research of American ginseng: with an example of colorectal cancer]," *Yao Xue Xue Bao*. 2013 Jul; 48 (7): 986-92.

[148] Poudyal D, Cui X, Le PM, Hofseth AB, Windust A, Nagarkatti M, Nagarkatti PS, Schetter AJ, Harris CC, Hofseth LJ. "A key role of microRNA-29b for the suppression of colon cancer cell migration by American ginseng," *PLoS One*. 2013 Oct 9; 8 (10): e75034. doi: 10.1371/journal.pone.0075034. eCollection 2013.

[149] 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; 65: 357-61. doi: 10.1016/j.ijbiomac.2014.01.046. Epub 2014 Jan 25.

[150] Yu C, Wen XD, Zhang Z, Zhang CF, Wu X, He X, Liao Y, Wu N, Wang CZ, Du W, He TC, Yuan CS. "American ginseng significantly reduced the progression of high-fat-diet-enhanced colon carcinogenesis in Apc (Min/+) mice," *J Ginseng Res*. 2015 Jul; 39 (3): 230-7. doi: 10.1016/j.jgr.2014.12.004. Epub 2015 Jan 10.

[151] Wang CZ, Huang WH, Zhang CF, Wan JY, Wang Y, Yu C, Williams S, He TC, Du W, Musch MW, Chang EB, Yuan CS. "Role of intestinal microbiome in American ginseng-mediated colon cancer prevention in high fat diet-fed AOM/DSS mice [corrected]," *Clin Transl Oncol*. 2018.

[152] Xie G, Wang CZ, Yu C, Qiu Y, Wen XD, Zhang CF, Yuan CS, Jia W. "Metabonomic Profiling Reveals Cancer Chemopreventive Effects of American Ginseng on Colon Carcinogenesis in Apc(Min/+) Mice," *J Proteome Res*. 2015 Aug 7; 14 (8): 3336-47. doi: 10.1021/acs.jproteome.5b00388. Epub 2015 Jul 10.

[153] Wang CZ, Yu C, Wen XD, Chen L, Zhang CF, Calway T, Qiu Y, Wang Y, Zhang Z, Anderson S, Wang Y, Jia W, Yuan CS. "American Ginseng Attenuates Colitis-Associated Colon Carcinogenesis in Mice: Impact on Gut Microbiota and Metabolomics," *Cancer Prev Res (Phila)*. 2016 Oct; 9 (10): 803-811. Epub 2016 Jul 21.

[154] Dai D, Zhang CF, Williams S, Yuan CS, Wang CZ. "Ginseng on Cancer: Potential Role in Modulating Inflammation-Mediated Angiogenesis," *Am J Chin Med*. 2017; 45 (1): 13-22. doi: 10.1142/S0192415X17500021. Epub 2017 Jan 9.

[155] Qu Y, Wang Z, Zhao F, Liu J, Zhang W, Li J, Song Z, Xu H. "AFM-detected apoptosis of hepatocellular carcinoma cells induced by American ginseng root water extract," *Micron. 2018 Jan; 104: 1-7. doi: 10.1016/j.micron.2017.10.003. Epub 2017 Oct 12*.

[156] Vohra S, Johnston BC, Laycock KL, Midodzi WK, Dhunnoo I, Harris E, Baydala L. "Safety and tolerability of North American ginseng extract in the treatment of pediatric upper respiratory tract infection: a phase II randomized, controlled trial of 2 dosing schedules," *Pediatrics*. 2008 Aug; 122 (2): e402-10. doi: 10.1542/peds.2007-2186.

[157] Chen EY, Hui CL. "HT1001, a proprietary North American ginseng extract, improves working memory in schizophrenia: a double-blind, placebo-controlled study," *Phytother Res*. 2012 Aug; 26 (8): 1166-72. doi: 10.1002/ptr.3700. Epub 2011 Dec 30.

[158] Lee TK, O'Brien KF, Wang W, Johnke RM, Sheng C, Benhabib SM, Wang T, Allison RR. "Radioprotective effect of American ginseng on human lymphocytes at 90 minutes postirradiation: a study of 40 cases," *J Altern Complement Med*. 2010 May; 16 (5): 561-7. doi: 10.1089/acm.2009.0590.

[159] Mucalo I, Jovanovski E, Rahelić D, Božikov V, Romić Z, 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. doi: 10.1016/j.jep.2013.08.015. Epub 2013 Aug 22.

[160] Ossoukhova A, Owen L, Savage K, Meyer M, Ibarra A, Roller M, Pipingas A, Wesnes K, Scholey A. "Improved working memory performance following administration of a single dose of American ginseng (*Panax quinquefolius L*.) to healthy middle-age adults, *Hum Psychopharmacol*. 2015 Mar; 30 (2): 108-22. doi: 10.1002/hup.2463.

[161] Barton DL, Soori GS, Bauer BA, Sloan JA, Johnson PA, Figueras C, Duane S, Mattar B, Liu H, Atherton PJ, Christensen B, Loprinzi CL. "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. doi: 10.1007/s00520-009-0642-2. Epub 2009 May 6.

[162] Chang YD, Smith J, Portman D, Kim R, Oberoi-Jassal R, Rajasekhara S1, Davis M. "Single Institute Experience With Methylphenidate and American Ginseng in Cancer-Related Fatigue," *Am J Hosp Palliat Care*. 2018 Jan; 35 (1): 144-150. doi: 10.1177/1049909117695733. Epub 2017 Mar 16.

[163] Szeto YT, Sin YS, Pak SC, Kalle W. "American ginseng tea protects cellular DNA within 2 h from consumption: results of a pilot study in healthy human volunteers," *Int J Food Sci Nutr*. 2015; 66 (7): 815-8. doi: 10.3109/09637486.2015.1088937. Epub 2015 Sep 22.

[164] 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*. 2017 Jul 7. doi: 10.1007/s00394-017-1496-x. [Epub ahead of print]

[165] Mucalo I, Jovanovski E, Vuksan V, Božikov V, Romić Z, Rahelić D. "American Ginseng Extract (*Panax quinquefolius L*.) Is Safe in Long-Term Use in Type 2 Diabetic Patients," *Evid Based Complement Alternat Med*. 2014; 2014: 969168. doi: 10.1155/2014/969168. Epub 2014 May 7.

[166] National Center for Complementary and Integrative Health, US National Institutes of Health, Bethesda, MD. September 2016. Retrieved 10 February 2017.

[167] Duda RB, Taback B, Kessel B, et al. "pS2 expression induced by American ginseng in MCF-7 breast cancer cells," *Ann Surg Oncol*. 1996; 3 (6): 515–520.

[168] Chang, Y. S., Pezzuto, J. M., Fong, H. H., Farnsworth, N. R., 1986. "Evaluation of the mutagenic potential of American ginseng (*Panax quinquefolius*)," *Planta Med*. 4, 338e339.

[169] Wang, Zengui; Huang, Linfang (March 2015). "Panax quinquefolius: An overview of the contaminants," *Phytochemistry Letters*. 11: 89–94. doi: 10.1016/j.phytol.2014.11.013.

[170] King ML, Adler SR, Murphy LL. "Extraction-dependent effects of American ginseng (*Panax quinquefolium*) on human breast cancer cell proliferation and estrogen receptor activation," *Integr Cancer Ther*. 2006; 5 (3): 236–243.

[171] Qi LW, Wang CZ, Yuan CS. "Ginsenosides from American ginseng: chemical and pharmacological diversity," *Phytochemistry*. 2011 Jun; 72 (8): 689-99. doi: 10.1016/j.phytochem.2011.02.012. Epub 2011 Mar 9.