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 ₄₇ H ₇₈ 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 ₄₇ H ₇₈ 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 ₄₇ H ₇₈ O ₁₅
58	F-D	glc	H	glc	(6)	C ₄₇ H ₇₈ 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 ₅₀ H ₈₂ O ₁₁
62	F-C	H	O-glc ² →rha	H	(7)	C ₄₇ H ₇₈ O ₁₅
63	QF-L ₃	glc ² →glc	H	glc ⁶ →arap	(8)	C ₅₄ H ₉₂ O ₂₃
64	QF-L ₂	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 ₃₀ H ₅₀ O ₈
72	G-RK ₁	glc ² →glc	H	C ₄₂ H ₇₀ O ₁₂
80	G-RK ₂	glc	H	C ₃₀ H ₅₀ 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 ₇₈ O ₁₉
73	G-RG ₅	glc ² →glc	H	C ₄₂ H ₆₈ O ₁₄
81	G-RH ₃	glc	H	C ₃₀ H ₅₀ 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- β -synthase; CGL, cystathionine- γ -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]
	Rg1	Stimulatory effects on CNS	Rat	[53]
		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 synapsin [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 (A β) peptides (A β 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 H₂O₂ 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 ($+1.85 \pm 2.13$ μ mol/L; $p < 0.03$), and produced a mean percent end-difference of $-12.3 \pm 3.9\%$ in LDL-C and $-13.9 \pm 5.8\%$ 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: $80\% \geq 2$, $60\% \geq 3$, and $46.7\% \geq 4$). 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.

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