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Repercussions of pathway inhibition response of Panaxginseng fractions ameliorate cardiac dysfunction in hypertensive model rats

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Abstract---This study examined the preventive and therapeutic benefits of various *Panax* ginseng fractions against NG-nitro-L-arginine methyl ester (L-NAME)-induced hypertension in rats. Rats injected with L-NAME plus vehicle exhibited persistently elevated SBP, serum concentrations of the cardiac injury biomarkers creatine kinase (CK), CK-MB, and troponin, total cholesterol, triglyceride (TG), low-density lipoprotein (LDL), and interleukin (IL)-6, but lower high-density lipoprotein (HDL) compared to the vehicle control group. Furthermore, L-NAME disrupted the normal histological structure and function of rat cardiac tissue. All ginseng fractions and losartan restored SBP to a normal level, reversed the changes in CK, CK-MB, troponin, total cholesterol, TG, HDL, and LDH, and preserved normal myocardial histology, with the WGF demonstrating the greatest cardioprotective and antihypertensive effects. Compounds within multiple ginseng fractions, but especially the aqueous fraction, possess potent and effective antihypertensive, antilipidemic, anti-inflammatory, and cardioprotective properties.

Keywords---*Panax* ginseng, L-NAME, hypertension, histology, cholesterol, antihypertensive.

Introduction

Hypertension (HTN) is a major global health challenge as it is highly prevalent and a strong risk factor for heart failure, myocardial infarction, and stroke. Chronic HTN induces abnormal extracellular matrix (ECM) deposition, oxidative stress, and inflammation within the vascular wall, processes that interact to initiate fibrotic responses that ultimately reduce vessel patency and oxygen transport capacity (Kalra *et al.* 2020 and Jan-On *et al.* 2020). During this pathogenic cascade, ECM-producing cells such as fibroblasts proliferate and differentiate into myofibroblasts, which in turn are major contributors to the fibrosis process (Murphy *et al.* 2015). Interleukin-6 (IL-6) is a multifunctional pro-inflammatory cytokine that contributes to fibrosis by promoting myofibroblast differentiation and ECM protein synthesis. At the molecular level, IL-6 upregulates transforming growth factor (TGF)-1 synthesis, which in turn activates the Smad3 signaling pathway, a major regulator of cardiac fibroblast proliferation and differentiation. Under HTN, myocardial hypertrophy is induced to maintain normal heart function (Ma *et al.* 2012). In addition, TGF- β 1 promotes the fibrogenic effects of the rennin-angiotensin system (RAS) through angiotensin receptor 1 (AT1) in many conditions like tubulointerstitial nephritis, myocardial infarction, and systemic sclerosis (Murphy *et al.* 2015). Conversely, inhibition of these pro-

inflammatory and fibrogenic signaling pathways is a promising strategy to prevent vascular damage, cardiac hypertrophy, and heart failure due to HTN.

Serum troponin, creatine kinase (CK), and CK-MB are widely used as biomarkers for cardiac cell injury and heart dysfunction under HTN (Wu *et al.* 2021). Further, HTN can be induced experimentally in animals by injection of the nitric oxide synthase (NOS) inhibitor NG-nitro-L-arginine methyl ester (L-NAME), and this model is widely accepted for assessing HTN-related end-organ damage (Ramanathan and Thekkumalai 2014; Adedara *et al.* 2018 and Torres-Narváez *et al.* 2019). At the cellular and molecular levels, L-NAME causes interstitial and perivascular fibrosis, as well as structural alterations in the heart due to cardiomyocyte hypertrophy and increased cardiomyocyte cell size, thereby recapitulating the major pathogenic events in HTN-associated cardiovascular disease. For more than 2000 years, raw ginseng and various extracts have been used in traditional medicinal systems to relieve fatigue and inflammation among other afflictions.

According to the Asian pharmacopoeia, ginseng extracts contain active constituents such as ginsenosides (saponins) and acidic polysaccharides as well as phenolic and polyacetylene components. The ginsenosides Rg3, Rg5, and Rk1 are widely believed to be the major bioactive ingredients (Kim 2016 and Hong *et al.* 2021), but it is likely that numerous additional ginseng-derived bioactive compounds remain unidentified. Ginseng extracts have demonstrated anti-inflammatory, antioxidant, anti-stress, anticancer, and cardioprotectant activities (Lee and Rhee 2017) as well as anti-fatigue, anti-diabetic, immunoregulatory, and atheroprotective actions (Patel and Rauf 2017). Ginseng may also modulate blood pressure, but results are inconsistent, with several studies indicating that ginseng elevates blood pressure and others reporting an antihypertensive effect (Miller 1998). Moreover, clinical trials on the effects of ginseng on blood pressure have been inconclusive (Han *et al.* 1998). These inconsistencies may be attributable to the reciprocal effects of different ginsenosides. The goal of this study is to examine if different ginseng extracts can protect against L-NAME-induced hypertension and ensuing cardiac dysfunction.

Materials and Procedures

Drugs and reagents

L-NAME was purchased from Sigma Chemical (St Louis, MI, USA) and dissolved in distilled water for injection. Losartan was purchased from a local pharmacy in Giza, Egypt. ELISA kits (P.R.C.) were purchased from Elabscience Biotechnology Co. All other reagents were of the highest analytical quality available. Panax ginseng grown in Vietnam was purchased from a local market in Cairo, Egypt (Haraz Company).

Instruments used for measuring blood pressure and cardiac functions

Blood pressure was measured using a tail cuff (ML 125 NIBP, AD Instruments, Australia) with transducer (TR1201, Pan lab, Spain) and monitor (LE501, LETICA Scientific Instruments, Spain). The rat electrocardiogram (ECG) was

measured using a Power Lab T 26, ML 856 amplifier (AD Instruments, Australia) and MLA 1515 cables (AD Instruments, Australia). To facilitate blood pressure measures, animals were first warmed in a thermostatically controlled heating cabinet (UGO Basile, Italy).

Animals

Female albino rats (13–15 weeks of age and weighing 150–170 g) were provided by the Animal House Colony of the National Research Centre in Cairo, Egypt. Animals were acclimated for one week in a specialized pathogen-free barrier area and then transferred to the National Research Centre animal facility breeding colony. Rats were housed under controlled temperature (25°C), humidity (55%) and 12 h/12 h light/dark cycle with free access to a regular laboratory diet and tap water prior to and throughout the experimental period. All animal procedures were approved by the National Research Center Ethics Committee and conducted in accordance with the institutional guidelines for the correct care and use of laboratory animals (NIH bulletin No. 85–23, updated 1985).

Preparation and fractionation of ginseng extracts

Panax ginseng plant materials were purchased fresh and rinsed multiple times with distilled water before drying in the shade for 8 days at room temperature. A high-powered blender was used to grind ginseng samples into powder (IKA-Laboratechnik, Germany). The milled powder (250 g) was extracted overnight with 75% (v/v) aqueous ethanol. The plant–solvent mixture was filtered and dried under reduced pressure using a Rotavapor (Buchi, Flawil, Switzerland) and then fractionated by solvent–solvent extraction into a butanol ginseng fraction (GBF), ethanol ginseng fraction (GEF), and distilled water ginseng fraction (GWF) fraction. All three fractions were concentrated and dried under reduced pressure in a rotary evaporator and then stored at 4°C. Chemical analyses were conducted by gas chromatography/mass spectroscopy (GC/MS) as described (Ragab *et al.* 2021).

Drug testing protocol

Seventy mature female rats were divided randomly into the following seven groups of 10: Saline Control; L-NAME (50 mg/kg b.wt in distilled water 5 days per week for 4 weeks (Kalra *et al.* 2020); L-NAME + crude ginseng fraction (CGF, 100 mg/kg b.wt dissolved in distilled water and administered orally on the same days as L-NAME injection); L-NAME+GWF (100 mg/kg b.wt water ginseng fraction administered orally as above); L-NAME+GEF (100 mg/kg b.wt in distilled water and administered orally); L-NAME+GBF (100 mg/kg b.wt in distilled water and administered orally (Wunpathe *et al.* 2020); L-NAME+Losartan (LOS, 30 mg/kg b.wt in distilled water and administered orally (Chen *et al.* 2015). Heart function was assessed by ECG and left ventricular pressure measurements at the end of the 4-week therapy period. Blood samples and heart specimens were also taken 24 hours following the last drug injection.

Biochemical assays

Lipid profiles (cholesterol, TG, HDL and LDL)

Serum cholesterol, TG, HDL, and LDL levels were estimated using Biodiagnostic kits (Dokki, Egypt) following the manufacturer's recommendations.

Enzyme-linked immunosorbent assay biomarkers

Serum cardiac biomarkers (CK, CK-MB, and troponin) and IL-6 were measured using Enzyme-Linked Immunosorbent Assay (ELISA) kits purchased from NOVA (Beijing, China).

In vivo assessments of the cardiovascular function

Blood pressure was measured in conscious rats and ECG under urethane anesthesia using the equipment described in Section 2.2.

Measurement of arterial SBP

SBP was measured non-invasively using the tail cuff method. Briefly, animals were warmed for 30 minutes at 28°C in a thermostatically controlled heating cabinet for better detection of tail artery pulse. Then, the tail was passed through a miniaturized inflatable cuff and a tail cuff sensor attached to an amplifier. The cuff was inflated until the pulse disappeared and the inflation pressure (equal to systolic pressure at the tail) was measured by the sensor.

Electrocardiographic (ECG) recordings

Rats were anesthetized by intramuscular injection of 0.6 mL/100 g.bw urethane (25% solution dissolved in distilled water) prior to recordings

Histopathology

Heart tissues were fixed in 10% neutral buffered formalin, washed, dehydrated in gradient alcohol (80%, 90%, and 100%), cleared in xylene, embedded in paraffin, and cut into 5–6 μ m sections. Section were then deparaffinized in xylene, stained with hematoxylin and eosin (H&E), and photographed under a light microscope (Olympus, Hamburg, Germany).

Statistical analysis (section 2.8)

All results are expressed as mean \pm standard error of the mean (SEM) based on results of the X test for normality. Treatment group means were compared by one-way analysis of variance with post hoc least significant difference tests for pair-wise comparisons (Armitage and Berry 1987). All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS), version 21 (Supplier). A $P < 0.05$ was considered statistically significant.

Results

Identification of ginseng fraction components by GC/MS

Eight-five major components were identified in the three fractions. ethanol fraction demonstrated as largest percent, 99.79% of the total fraction, then the water fraction was 99.73%, and finally butanol fraction was 99.09%, in previous research. The proportion (ratio) of carboxylic acids was higher in the GBF (21.40%) than the GEF (12.34%) or GWF (10.25%). The proportion of alcohols was also greater in the GBF (11.57%) than the GWF (8.08%) and GEF (2.92%). Similarly, the proportion of amino acids was higher in the GBF (10.15%) than the GEF (4.60%) and GWF (4.26%), as was the proportion of fatty acids (8.83%) compared to the GWF (0.68%) and GEF (0.25%). Amines, amides, furans, and ketones were all present at trace amounts in all three fractions (less than 1%). Ginseng has a high carbohydrate content in general, and carbohydrates accounted for 79.00% of compounds in the GEF, 74.45% of those in the GWF, and 45.22% of those in the GBF (Ragab *et al.* 2021).

Effects of ginseng fractions on cardiac functions and blood pressure in hypertensive rats

Effects of the crude ginseng extract and the three ginseng fractions on cardiac function parameters and SBP in the rat hypertensive model are summarized in Tables (1) and (2), while effects on the ECG are shown in Figure 1.

Ginseng fractions reversed L-NAME-induced electrocardiogram abnormalities

Heart rate was significantly ($P < 0.05$) higher in the L-NAME+vehicle group compared to the untreated control group. In addition, the P-R Interval, P Duration, and P Amplitude were all significantly greater in the L-NAME+vehicle group. Administration of all ginseng extracts significantly reduced the P-R Interval and P duration compared to the L-NAME+vehicle group. Similarly, R Amplitude, ST Height, and T Amplitude were significantly elevated in the L-NAME+vehicle group, and these effects were also reversed by all ginseng fractions. Further, the effects of the GWF, GEF, and GBF on these ECG parameters were superior to those of the crude fraction.

Ginseng fractions ameliorated L-NAME-induced HTN

As expected, SBP was significantly elevated in the L-NAME+vehicle group compared to the control group, and ginseng fractions significantly reversed this hypertensive effect. Moreover, GWF, GEF, and GBF demonstrated superior antihypertensive properties compared to the crude fraction and the clinical antihypertensive losartan.

Table 1
Effects of ginseng fractions on heart rate, PR interval, P duration, and P amplitude of hypertensive rats

Group	Heart rate (BPM)	P-R interval (s)	P duration (s)	P amplitude (mV)
Control	315 ± 1.5	0.04584 ± 0.0007	0.01156 ± 0.00014	0.01383 ± 0.00012
L-NAME+ vehicle	409.6 ± 2.1 ^a	0.04937 ± 0.0007 ^a	0.01412 ± 0.00087 ^a	0.06915 ± 0.00088 ^a
L-NAME+crude	407.6 ± 1.5 ^a	0.04937 ± 0.0003 ^a	0.01842 ± 0.00029 ^{ab}	0.01093 ± 0.00043 ^{ab}
L-NAME+GWF	351.0 ± 1.3 ^{ab}	0.04034 ± 0.0002 ^{ab}	0.01366 ± 0.00014 ^a	0.02858 ± 0.00058 ^{ab}
L-NAME+GEF	412.6 ± 1.4 ^a	0.04409 ± 0.0001 ^b	0.01236 ± 0.00098 ^b	0.06495 ± 0.00079 ^{ab}
L-NAME+GBF	424.6 ± 1.7 ^{ab}	0.04124 ± 0.0004 ^{ab}	0.01481 ± 0.00020 ^a	0.06485 ± 0.00034 ^{ab}
L-NAME+LOS	344.0 ± 1.9 ^{ab}	0.04724 ± 0.0003 ^b	0.01850 ± 0.00095 ^{ab}	0.04848 ± 0.00010 ^{ab}

Data expressed as mean ± standard error of the mean (SEM) for 10 animals/group. L-NAME, NG-nitro-L-arginine methyl ester; GCF, ginseng crude fraction; GWF, ginseng water fraction; GEF, ginseng ethanol fraction; GBF, ginseng butanol fraction; LOS, losartan

a: P < 0.05 vs. control group.

b: P < 0.05 vs. hypertensive (L-NAME+vehicle) group.

Table 2
Effects of ginseng fractions on QRS interval, R amplitude, ST height, T Amplitude and systolic blood pressure of hypertensive rats

Group	QRS Interval (s)	R Amplitude (mV)	ST Height (mV)	T Amplitude (mV)	Systolic Blood Pressure
Control	0.01371 ± 0.0001	0.5136 ± 0.0023	0.04111 ± 0.00039	0.1546 ± 0.0011	104.3 ± 1.08
L-NAME+ vehicle	0.01364 ± 0.00012	0.6672 ± 0.0036 ^a	0.1334 ± 0.0015 ^a	0.2434 ± 0.00092 ^a	174.6 ± 2.30 ^a
L-NAME+ crude	0.0131 ± 0.00015 ^a	0.0797 ± 0.0005 ^{ab}	0.1244 ± 0.0014 ^{ab}	0.2583 ± 0.0012 ^{ab}	140.6 ± 7.72 ^{ab}
L-NAME+ GWF	0.01276 ± 0.0006 ^a	0.6060 ± 0.0025 ^{ab}	0.1040 ± 0.0013 ^{ab}	0.148 ± 0.0025 ^{ab}	107.3 ± 5.52 ^b
L-NAME+ GEF	0.01724 ± 0.00088 ^{ab}	0.4991 ± 0.0045 ^b	0.006425 ± 0.00024 ^{ab}	0.1174 ± 0.0014 ^{ab}	104.3 ± 2.08 ^b
L-NAME+ GBF	0.01264 ± 0.00035 ^{ab}	0.4816 ± 0.0031 ^{ab}	0.08625 ± 0.00066 ^{ab}	0.1753 ± 0.0017 ^{ab}	116.0 ± 6.04 ^b
L-NAME+ LOS	0.01697 ± 0.00011 ^{ab}	0.4639 ± 0.0057 ^{ab}	0.1053 ± 0.0012 ^{ab}	0.1816 ± 0.0010 ^{ab}	121.0 ± 1.85 ^b

Data are expressed as mean ± standard error of the mean (SEM) for 10 animals/group.

a: $P < 0.05$ vs. control group.
 b: $P < 0.05$ vs. hypertensive group.

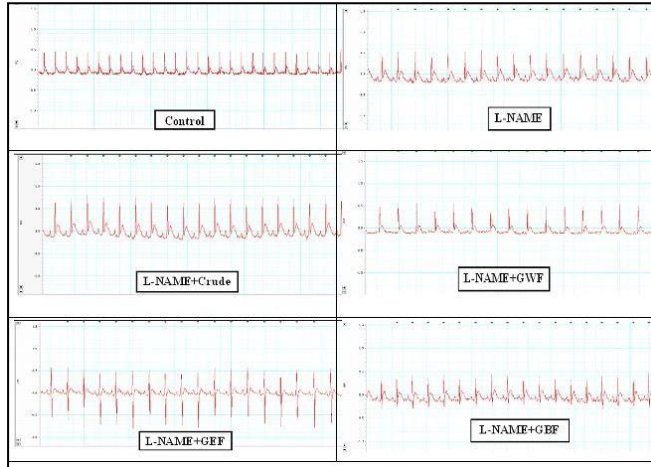
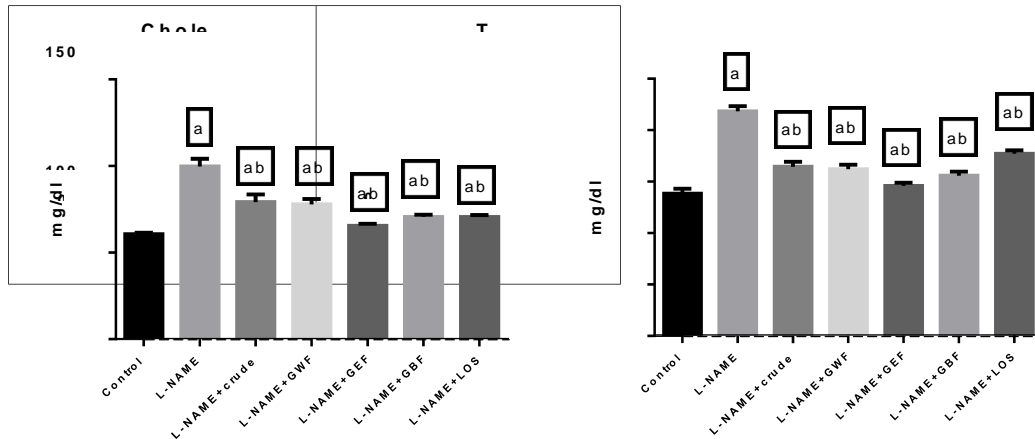


Figure 1. Electrocardiograms of the indicated treatment groups. GWF, ginseng water fraction; GEF, a ginseng ethanol fraction; GBF, ginseng butanol fraction; LOS, losartan

Ginseng fractions normalized serum lipid profiles in hypertensive rats

Total blood total cholesterol was elevated by 64.8%, triglycerides by 57.9%, and LDL-cholesterol by 80.4% while HDL-cholesterol was reduced by 47.8% in hypertensive rats compared to controls (all $P < 0.05$) (Fig. 2). All three ginseng fractions (100 mg/kg.bw) significantly reversed the rise in total cholesterol, triglycerides, and LDL-cholesterol as well as the fall in HDL-cholesterol (Fig. 2).



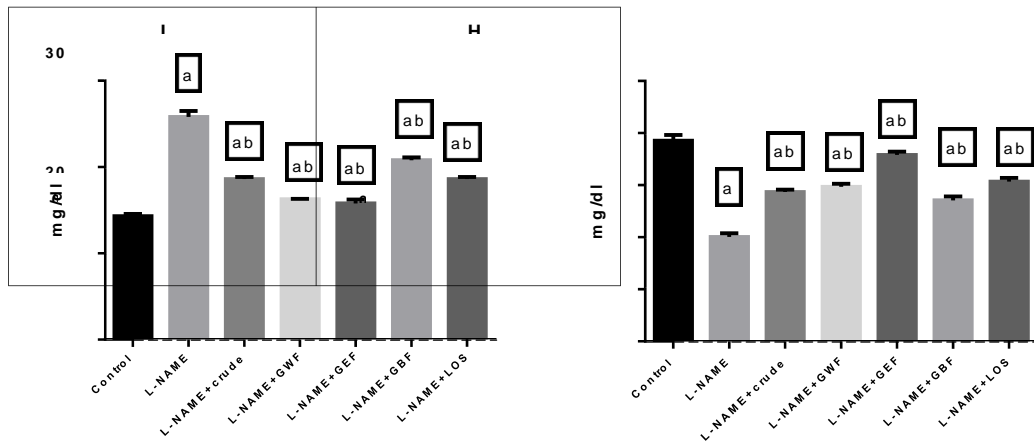
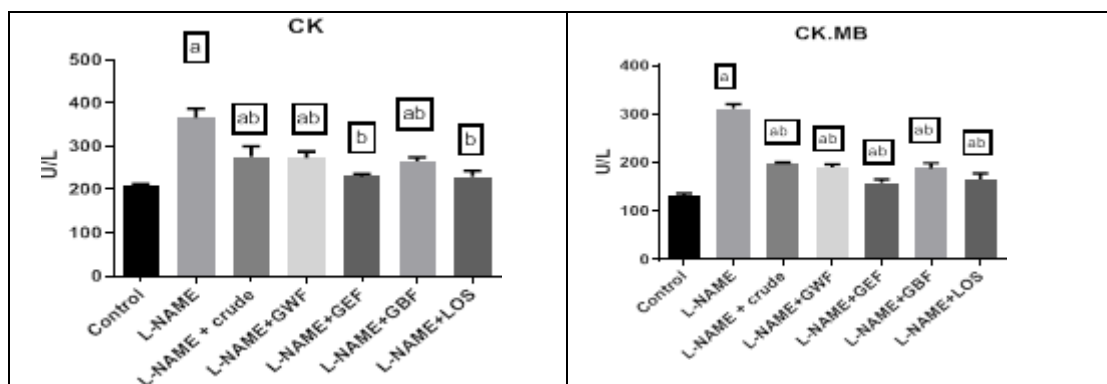


Figure 2. Ginseng fractions improved lipid profiles in hypertensive rats. Data are presented as mean \pm SEM. Treatments with superscript a are significantly different from the vehicle control group, and treatments with superscript b are significantly different from the L-NAME+vehicle group (disease group) ($P < 0.05$). GCF, ginseng crude fraction; GWF, ginseng water fraction; GEF, ginseng ethanol fraction; GBF, ginseng butanol fraction; LOS, losartan

Ginseng fractions reversed serum elevations of cardiac injury and inflammation biomarkers in hypertensive rats

Serum concentrations of cardiac injury biomarkers CK, CK-MB, and troponin 1 were significantly elevated in the L-NAME+vehicle group compared to the untreated control group. These increases were partially reversed by all ginseng fractions, consistent with cardioprotective efficacy. Further, all fractions reversed the increasing in IL-6 observed in the L-NAME+vehicle group (51.1%), indicating anti-inflammatory activity (Fig. 3).



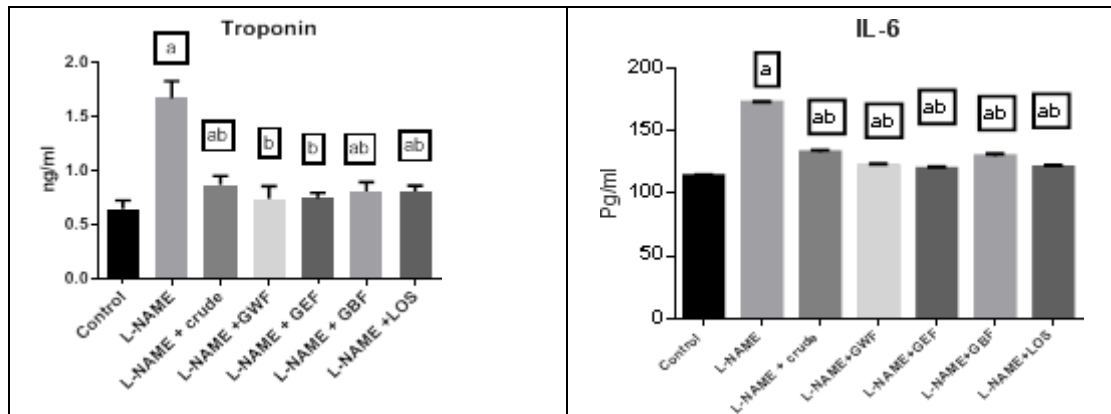
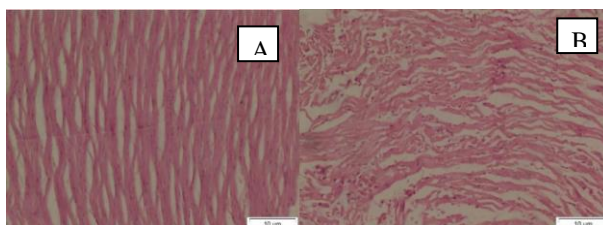


Figure 3. Ginseng fractions reduced myocardial injury and inflammation in hypertensive rats. Data are presented as mean \pm SEM. Treatments with superscript a are statistically different from the vehicle control group and treatments with superscript b are statistically different from the L-NAME+vehicle (disease) group ($P < 0.05$). Abbreviations are the same as in Figure (2)

Ginseng water fraction reversed L-NAME-induced histopathology in heart tissue of hypertensive rats

Longitudinal H&E-stained sections from control rat myocardium exhibited the expected striate appearance due to the parallel orientation of cardiomyocytes with occasional branching. Also as expected, individual cells exhibited centrally located nuclei, occasional bi-nucleation, and periodic separation by intercalated discs (Fig. 4A). In contrast, myocardial sections from hypertensive rats revealed aberrant separation of muscle fibers due to intracardial congestion and hemorrhage. Foci of contraction band necrosis were also observed (Fig. 4B). Myocardial sections from hypertensive rats treated with GBF revealed individual myocardial cells arranged in diffuse bundles within a connective tissue framework (Fig. 4C), while sections from hypertensive rats receiving GEF exhibited markedly disoriented muscle fibers, sarcoplasmic vacuolation, and fiber degeneration (Fig. 4D). However, sections from hypertensive rats receiving GWF showed improved fiber architecture, fewer regions of fiber separation, and normal nuclei (Fig. 5E).



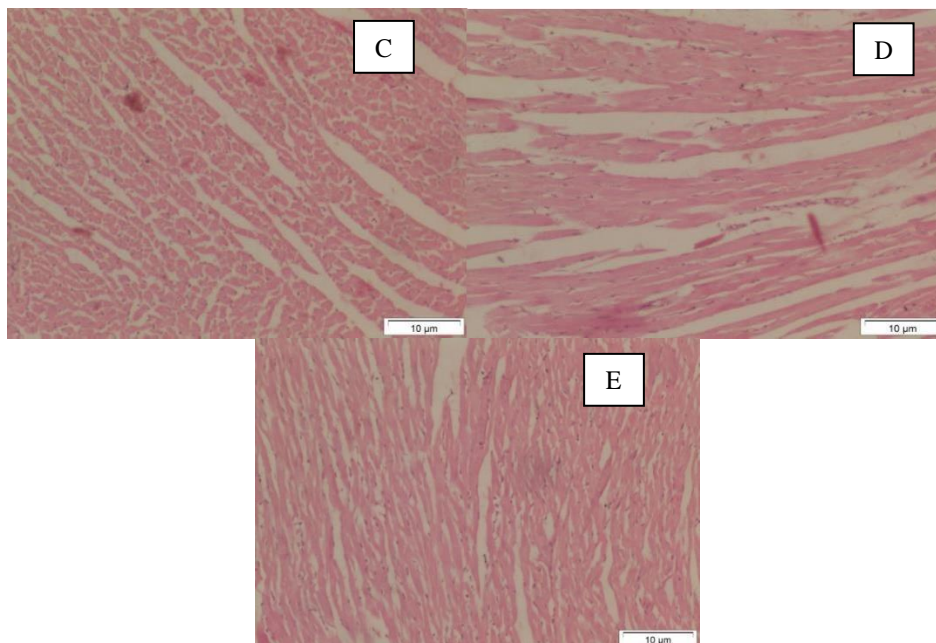


Figure 4. The ginseng water fraction partially restores normal myocardial histology in hypertensive rats. (A) Longitudinal section of heart from a control rat showing healthy parallel-oriented myocardial cells with intact intercalated discs (arrows), acidophilic sarcoplasm, and centrally located nuclei. B) Longitudinal section from a hypertensive rat showing separation of muscle fibers and intracardial congestion, hemorrhage, and foci of contraction band necrosis. C) Longitudinal section from a hypertensive rat receiving GBF showing individual myocardial cells arranged in diffuse bundles within a connective tissue framework. D) Longitudinal section from a hypertensive rat given GEF showing disoriented muscle fibers, sarcoplasmic vacuolation, and fiber degeneration. E) Longitudinal section from a hypertensive rat receiving GWF showing improved fiber architecture and normal nuclei (Scale bar:10 μ m). Abbreviations are the same as in Figure (2) and (3)

Discussion

Chronic hypertension induced by L-NAME resulted in inflammation, dyslipidemia, fibrosis, and cardiovascular remodeling, and all of these changes were reversed by a ginseng water extract. Further, ethanol and butanol extracts also markedly reduced hypertension, dyslipidemia, and inflammation, and partially protected myocardial tissue from remodeling. The antihypertensive and antilipidemic efficacies of these extracts were comparable to a clinical antihypertensive agent (losartan). Further studies are warranted to identify the antihypertensive, antilipidemic, and cardioprotective compounds in ginseng extract.

The stress on perivascular and heart cells cause by HTN induces inflammation, cardiac modeling, and cell death, which can be detected by inflammatory markers and myocardial cell contents in serum. A causal association with HTN is supported by the presence of these biomarkers in animals treated with

vasoconstrictor drugs like Ang II and L-NAME (Wunpathe *et al.* 2020). Nitro-arginine (L-NAME) induces hypertension by blocking NOS, the enzyme responsible for production of the powerful vasodilator NO (Opie *et al.* 2006), leading to endothelial dysfunction, fibrosis, cardiac remodeling, and deterioration of cardiac function (Veerappan and Senthilkumar 2015). Prolonged L-NAME treatment induced an inflammatory response in rat heart as evidenced by increased IL-6 as well as cardiac cell death as evidenced by elevated serum CK, CK-MB and troponin 1, and by direct histopathological observation. These findings are also consistent with a prior study reporting that L-NAME administration increased IL-1, IL-6, and TNF- α mRNA expression in rat heart concomitant with induction of HTN (Miguel-Carrasco *et al.* 2008).

Furthermore, the current findings are consistent with Rossoni *et al.* (Rossoni *et al.* 2007), who found that L-NAME increased CK and troponin 1 leakage from myocardium. The L-NAME treatment group also exhibited considerably greater levels of total cholesterol, triglycerides, and LDL in serum than the control group, consistent with Aldubayan *et al.* (Aldubayan *et al.* 2020). On the other hand, L-NAME reduced serum HDL (good cholesterol) (Bilanda *et al.* 2017), possibly by reducing the oxidation of fatty acids (Li *et al.* 2020). These responses were substantially or partially attenuated by all three ginseng fractions as well as by losartan, indicating that these extracts have hypotriglyceridemic and hypocholesterolemic activities as well as antihypertensive activity (Lu *et al.* 2019 and Li *et al.* 2020). These dual effects are critical as dyslipidemia in addition to HTN is a major risk factor for cardiac events.

Losartan is a nonpeptide angiotensin receptor II (Ang II) antagonist that lowers blood pressure and is well tolerated as it also inhibits angiotensin II binding to the type 1 receptor. Losartan has been shown to reduce hypertension, prevent cardiovascular morbidity and mortality, and protect heart function by preventing the deleterious effects on Ang II on ischemic/reperfused myocardium (EL Desoky *et al.* 2017). Similarly, the GWF had remarkable cardioprotective efficacy not shared by the other fractions despite comparable antihypertensive activity, suggesting the presence of additional cardioprotective agents. A therapeutic dose of losartan also improved lipid profiles, in accord with several studies of essential hypertension patients in which losartan reduced total cholesterol, LDL, and triglycerides (Kyvelou *et al.* 2006 and Sivasubramaniam and Kumarasamy 2017). Moreover, one such study (Kyvelou *et al.* 2006) also found that losartan can increase HDL.

It is uncertain if the therapeutic effects of ginseng and losartan are mediated by similar mechanisms. Angiotensin receptor blockers regulate lipid metabolism by activation of PPAR gamma and an ensuing interaction between lipid metabolism and angiotensin signaling pathways. Furthermore, increased uric acid production is linked to triglyceride synthesis, and there is a negative relationship between HDL-c and uric acid in hypertensive patients with dyslipidemia. Further study is required to determine if similar processes contribute to the effects of ginseng extract. Losartan also reduced the L-NAME-induced increases in serum markers of cardiac injury (CK, CK-MB and troponin1) as well as the inflammatory biomarker IL-6. Moreover, losartan diminished activities of antioxidant enzymes. These findings are in agreement with Al-Saad *et al.* (Al Saad *et al.* 2020) who

reported that losartan prevented the aberrant cardiac, hepatic, and renal remodeling associated with chronic HTN by preventing oxidative damage, inflammatory cytokine elevation, and ensuing necrosis through angiotensin receptor blockade. Angiotensin receptor II can promote monocyte migration and local pro-inflammatory cytokine release. Furthermore, because Ang II promotes and regulates the generation of ROS and NO, inhibiting Ang II receptor type 1 (AT1R) could result in a significant reduction in systemic inflammation and oxidative stress (Mahmoudabady *et al.* 2015). According to de Gracia *et al.* (2000), losartan blocks the activity of systemic Ang II, thereby preventing L-NAME from causing hypertension. Losartan also decreased TNF- α expression, a sign of systemic inflammation, by reversing the effects of Ang II (Rosa *et al.* 2012).

Past research has shown that ginseng reduces arterial stiffness (Jovanovski *et al.* 2014) and blood pressure (Nagar *et al.* 2016), slows the progression of atherosclerotic lesions (Dou *et al.* 2012), regulates blood lipid profiles, and inhibits inflammatory factors. Our findings confirm that these extracts can counteract systolic blood pressure (SBP) elevation, pro-inflammatory cytokine IL-6 production, and cardiac injury in L-NAME-induced hypertensive rats, in addition to improving lipid profile (Lee *et al.* 2020). However, more research is needed to identify the precise bioactive ingredients for more targeted treatment. Ginseng contains a multitude of pharmaceutically active components, including ginsenosides (saponins), polyacetylenes, polyphenolic substances, and acidic polysaccharides. Ginsenosides Rg3, Rg5, and Rk are regarded as the most pharmaceutically active of these chemicals with well documented antihypertensive, antiatherosclerotic, and anti-inflammatory effects (Christensen 2009).

High LDL induced the inflammatory response and apoptosis of vascular endothelial cells through the NF- κ B, p38, and JNK pathways, and ginsenoside compounds reduce LDL and TG by blocking these pathways (Lu *et al.* 2019 and Li *et al.* 2020). Furthermore, these compounds can deplete plasma total cholesterol by downregulating cholesterol synthesis, lipoprotein assembly, or secretion, and by upregulating cholesterol transport and efflux (Li *et al.* 2020). They also reduced the expression of IL-1, IL-6, TNF- γ , NF- κ B, and G6Pase (Fan *et al.* 2019 and Yang *et al.* 2019). The water fraction produced the greatest reversal of endothelial dysfunction and vascular stiffness, in addition to effectively reducing blood pressure. Furthermore, we found that collagen deposition was reduced and dispersed bundles were contained within a connective tissue framework. These benefits of ginseng extracts can be explained in part by the presence of linoleic acid, citric acid, and malic acid, which reduce TG and LDL-cholesterol levels as well as the inflammatory mediators IL-6 and COX-2, leading to suppression of downstream inflammatory signaling pathways, such as caspase-1, NF- κ B, and MAPK cascades, and improved endothelial function in resistance arteries (John *et al.* 2018; Nunes *et al.* 2018 and Barragán-Zarate *et al.* 2020).

While the end effects were similar to the reference drug (Losartan), an angiotensin receptor blocker with a remarkable therapeutic effect against L-NAME-induced chronic HTN through prevention or attenuate the pro-inflammatory and pro-fibrotic markers (Chen *et al.* 2015), addition studies are needed to confirm the therapeutic mechanisms of these ginseng extracts. Collectively, these findings

strongly suggest that compounds contained in these ginseng fractions synergistically reduce extracellular matrix deposition, fibrosis, cardiomyocyte hypertrophy, and inflammation (Li *et al.* 2020), thereby preventing remodeling, heart failure, and infarction (Qin *et al.* 2019). These benefits may result from blockade of the RAS system, ultimately helping to maintain intact cardiac morphology and function (Wang *et al.* 2020).

Conclusion

Ginseng extracts demonstrated powerful antihypertensive, antilipidemic, anti-inflammatory, and cardioprotective effects in the L-NAME-induced rat model of chronic hypertension, with the water extract showing superior therapeutic efficacy. Further, antihypertensive and antilipidemic effects were comparable to the widely used clinical drug losartan.

Statements and Declarations

Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could influence the work reported in this paper.

Ethical Approval

This article does not contain any experiments on human participants. All animal experiments were approved by the institution ethics committee. or animals performed by any of the authors.

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Availability of data and material

The datasets generated and/or analyzed during the current study are included in this published manuscript.

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Authors' contributions

N.A.; S.H.M.; AS.G.S. and T.I.M. wrote the original draft of the manuscript. S.H.M. and N.A.A. revised the manuscript. AS.G.S. and T.I.M. performed the extract section, S.H.M.; N.A.A. and A.B.S. performed the experiments and analyzed the data. M.M.M. and A-R. H. F. performed pathology section N.S.A-L. performed Pharmacological Studies.

Ethics approval

All animal procedures were carried out with the agreement of the National Research Centre's Ethics Committee and in accordance with the National Research Centre's instructions for the correct care and use of laboratory animals (NIH bulletin No. 85–23, updated 1985).

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Consent for publication

All authors read and approved the final manuscript and submitted it for consideration for publication.

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