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Research Article

Developing a Herbal Cocktail for prevention of Stroke and cerebrovascular diseases

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ABSTRACT

Natural herbs have long been used in food supplements to promote health as healthy alternative to the various conditions/diseases as preventive medicine. A variety of herbs and prescriptions have been demonstrated to have neuroprotective effects *in vivo* and *in vitro* that may be relevant to the treatment of stroke.

The present study carried out to investigate the development of hyperlipidemia in response to a high fat diet (HFD) and to estimate the effect of 70% ethanolic extracts for herbal cocktail (*Artemisia Judaica 50mg/kg B.wt, Panax ginseng 50mg/kg B.wt, Salvia officinalis 100mg/kg B.wt and Polygonum multiflorum 400mg/kg B.wt*) on lipid profiles, oxidative stress markers, and inflammatory mediators in blood and liver tissue in rats. The anti-hyperlipidemic and antioxidant effect of herbal cocktail were studied high fat diet induced hyperlipidemic rats. Serum total lipid (TL), cholesterol (TC), triglycerides (TG), LDL and oxidative stress marker (MDA, GSSG, NO and 8-OH-dG) were significantly lowered by herbal cocktail. Herbal cocktail increased the activities of reduced glutathione (GSH) and HDL while significantly decreasing inflammatory mediators (TNF-α, IL1-β and IL-6). It could be concluded that HFD induced hyperlipidemia associated with a disturbed lipid profile, defective antioxidant stability, and high values of inflammatory mediators; this may have implications for the progress of obesity related problems. Treatment with individual herb and herbal cocktail improve obesity and its associated metabolic syndrome problems. Herbal cocktail has hypolipidaemic and antioxidant effects. Moreover, herbal cocktail might be a safe combination on the organs whose functions were examined, as a way to surmount the obesity state; and it has a distinct anti-obesity effect.

Keywords: *Artemisia Judaica, Panax ginseng, Salvia officinalis, Polygonum multiflorum*, *Antiobesity and High fat diet.*

INTRODUCTION:

Stroke is one of the leading causes of death. About 600,000 people experience a first-time stroke every year. Stroke ranks number three among all causes of death, after heart disease and cancer. Incidence of stroke has decreased between 1950 and 2004 from 7.6% in men and 6.2%in women (1950–1977) to 5.3% in men and 5.1% in women (1990–2004) **[1].** Major modifiable risk factor for stroke is hyperlipidemia. Dyslipidemia has long been recognized as a risk factor for coronary artery disease, but its role in stroke has become increasingly apparent over the past decade. Hyperlipidemia is a condition associated with increased level of lipids in plasma leading to various disorders including coronary artery disease. Hyperlipidemia is a highly predictive risk factor for atherosclerosis, coronary artery disease and cerebrovascular disease **[2].** In recent years, cardiovascular diseases such Atherosclerosis, that are caused as a result of hyperlipidemia elevate mortality percent, and the age of death has reduced, so reducing serum hyperlipidemia is very important; a 1% reduction in serum cholesterol concentration results in a 2% reduction in the prevalence of coronary artery diseases **[3].** It is clearly established that long-term consumption of a high fat diet accelerates the development of Coronary Heart Disease (CHD). Dietary cholesterol can

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increase the level of serum cholesterol to levels which can place an individual at increased risk for the development or exacerbation of atherosclerosis **[4].** Coronary Heart Disease (CHD) increases dramatically as the plasma concentration of LDL cholesterol increases. The approach of reducing dietary cholesterol suffers from two limitations, the first is that cholesterol is present in all animal fats and many people are unwilling to scarify their preferred diet. The second is that the liver and other tissues synthesize cholesterol de novo if the dietary supply is inadequate. Consequently, the development of methods for lowering LDL cholesterol levels has become a major focus of medical research. In recent years, many synthetic drugs have been used to treat cardiac problems. These drugs produce different side effects, depending on their mechanisms of action which may lead to severe complications **[5].** Hence present trend is diverting towards the screening of traditional herbal medicines to treat fatal diseases. The use of herbal medicine has become more prevalent, and the past few decades have witnessed a rapidly increasing demand worldwide. The range of medicinal plants is very diverse and it has been estimated that around 70,000 different plant species have been used at least once during the history of traditional medicine **[6].**

Artemisia genus (Asteraceae, Anthemideae, Artmisiianae) comprises hundreds (about 500) of different species, but its systematic classification remains discussed. In general five different subtaxa are considered **[7].** *Artemisia* have biological activates, including the inhibition of aflatoxin B1 bio-transformation to aflatoxin B1 **[8]** and potent protection effects on CCl_4 induced acute hepatotoxicity in rats **[9].**

Won-Sik *et al*., (2013) [10] showed that the ethanolic extract of *Artemisia* decrease cholesterol level for male SpragueDawley rats fed a high-fat diet (HFD) for 4 wk.

Ginseng is known to affect various tissues including nervous, cardiovascular, endocrine, and immune system tissues; its major physiologically active ingredients include ginsenosides, polysaccharides, amino acids, polyacetylenes, alkaloids, and phenolic compounds **[11].** A major class of active compounds related to the physiological activity of ginseng is the ginsenosides, which are divided into dammarane type and oleanane type, depending on the binding sugar moiety; research studies on ginseng have mainly studied the efficacy of saponins such as ginsenoside, although ginseng saponins have been reported to have relatively low antioxidant effects **[12].** According to recent studies, a hypolipidemic effect of Panax ginseng extract (PGE) is associated with decrease in total cholesterol (TC), triglycerides (TGs), low-density lipoprotein (LDL), Muscular Dystrophy Association (MDA) levels and an increase in high-density lipoprotein (HDL) level. Administration of PGE increased serum superoxide dismutase (SOD) and catalase (CAT) activities while decreased MDA level indicating that antioxidant potential of PGE might induce hypolipidemic effect as one of action mechanism **[13].** *Salvia officinalis* L. is a spice, popularly known as sage that belongs to the *Lamiaceae* family **[14].** In folk medicine, the leaves are mainly used, but the flowers and stems have also been used in infusions and alcoholic extracts for various therapeutic purposes.

Sage leaf contains tannic acid, oleic acid, ursonic acid, ursolic acid, niacin, nicotinamide, flavones, flavonoid glycosides, cornsole, cornsolic acid, fumaric acid, chlorogenic acid, caffeic acid, and estrogenic substances **[15].** Investigations have taken place into using sage as a treatment for hyperlipidemia and Alzheimer's disease **[16].** Antioxidants affect blood sugar and antioxidant properties of *Salvia officinalis L* (Sage) leaves are known **[17].** *Polygonum* extracts exhibited anti-obesity effects by suppressing lipogenesis in white adipose tissue and increasing antioxidant activity. Besides, its low toxicity in mice and its historical use suggested PE might be used as a safe anti-hyperlipidemia pharmaceutical **[18].** Plasma cholesterol, plasma triglyceride and low-density lipoprotein cholesterol increased, while very low-density lipoprotein cholesterol attenuated after treatment with a water-soluble fraction of *Polygonum multiflorum* (PM), suggesting PM might be applicable for the treatment of hyperlipidemia disease **[19].** In a high fat/cholesterol rabbit model, polydatin from *Polygonum cuspidatum* obviously decreased the serum levels of total cholesterol (TC), triglyceride (TG), and low-density lipoprotein cholesterol. Meanwhile, the ratio of TC and the liver coefficient were also reduced **[20].**

Herbal mixture seemed to be beneficial for the reduction of body weight and improvement of antioxidant status of the erythrocytes, and its anti-hyperlipidemic property was highly active for enhancing the profile of plasma lipids in rats.
Therefore, the aim of this study was to evaluate possible effects of different herbal cocktail on serum lipid profile, inflammatory mediators and liver oxidative stress marker of male rat which may reflect a specific allowances being a critical obstacle for Stroke and cerebrovascular diseases.

Material and methods

This study was carried out at animal physiology Lab., NODACR, Giza, Egypt starting from the first of July till the end of September 2015.

Extract preparation:

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Approximately 150 g of *Artemisia Judaica* leaf were extracted twice with 70% ethanol using a 2 h reflux extraction, and the extract was concentrated under reduced pressure. The concentrate was filtered, lyophilized, and subsequently stored at 4◦C. The yield of the dried extract from starting crude materials was 16.22% (w/w).

Approximately 100 g of *Panax ginseng* root were extracted twice with boiling water, filtered, evaporated in a rotary vacuum evaporator, and freeze-dried. The yield of the dried extract from starting crude materials was 21.07% (w/w).

Approximately 200 g of *Salvia officinalis* leaf were extracted twice with 70% ethanol using a 2 h reflux extraction, and the extract was concentrated under reduced pressure. The concentrate was filtered, lyophilized, and subsequently stored at 4◦C. The yield of the dried extract from starting crude materials was 18.81% (w/w).

Approximately 1500 g of *Polygonum multiflorum* root were extracted twice with 70% ethanol using a 2 h reflux extraction, and the extract was concentrated under reduced pressure. The concentrate was filtered, lyophilized, and subsequently stored at 4◦C. The yield of the dried extract from starting crude materials was 13.73% (w/w).

1. Experimental design

A total of ninety six rats (*Sprague Dawley)* were utilized in this study. The rats had an initial weight 200±20 g (9-12 weeks old). Rats were randomly divided into sixteen groups, each comprising six rats. The study was conducted for three months which included 60 days of feeding period and next 30 days of treatment period.

Group I served as normal control was fed with standard rat chow throughout the study. Group II to VII were fed with high-fat diet for 60 days during the feeding period and then the high-fat diet was replaced by standard diet for the next 30 days of treatment period. Rats were supplied food and water *ad libitum*.

Group I served as control received normal saline (5 ml/kg, per oral by oral feeding needle with tuberculin syringe) daily for 30 days.

Group II served as hyperlipidemic diet and received normal saline (5ml/kg, per oral by oral feeding needle with tuberculin syringe) daily for 30 days.

Group III served as hyperlipidemic diet and received *Artemisia Judaica* extract (50 mg/kg per oral by oral feeding needle with tuberculin syringe) daily for 30 days.

Group IV served as hyperlipidemic diet and received *Panax ginseng* extract (50 mg/kg per oral by oral feeding needle with tuberculin syringe) daily for 30 days.

Group V served as hyperlipidemic diet and received *Salvia officinalis* extract (100 mg/kg per oral by oral feeding needle with tuberculin syringe) daily for 30 days.

Group VI served as hyperlipidemic diet and received *Polygonum multiflorum* extract (400 mg/kg per oral by oral feeding needle with tuberculin syringe) daily for 30 days.

Group VII served as hyperlipidemic diet and received mixture of herbal extract (*Artemisia Judaica* + *Panax ginseng + Salvia officinalis + Polygonum multiflorum* 50, 50, 100 and 400 mg/kg b.wt respectively, by oral feeding needle with tuberculin syringe) daily for 30 days.

Induction of hyperlipidemia

High fat diet (HFD) showed in Table 1

Table 1: Composition of experimental diets according to nutrition requirement center (NRC, 1998) [21].. by Feed soft enterprise program 2010:

Formula Ingredients / kg	BD	HFD
Casein	5.0	5.0
Colic acid	2.0	2.0
Corn, Grain	57.8	32.8
Dical. Phos	0.1	0.1
DL-Methionine	0.1	0.1
L-Lysine HCl	0.1	0.1
Limestone	5.0	5.0
Methionine HA	0.1	0.1
Mineral Premix	0.1	0.1
Salt	1.0	1.0
Soybean Meal-44	23.7	28.7
Soybean Oil	5.0	25.0
Vitamin Premix	0.1	0.1

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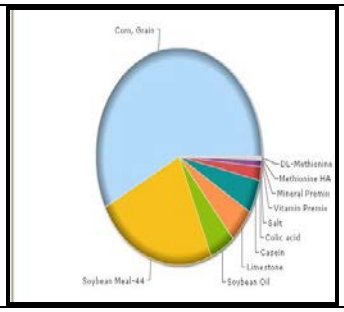
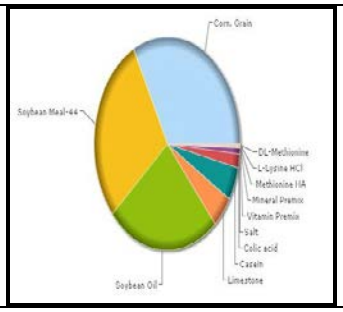
Composition chart		

Animals were cared in accordance with standard guidelines [22]. All blood samples were collected within one hour period between 8:00am and 9:00 am. Twelve hours fasted blood samples were collected under light ether anesthesia by retro orbital puncture. Blood samples were collected after 30 days of the treatment period. These blood samples were used for serum lipid analysis and inflammatory mediators. Then in the morning of the 90th day animal groups were sacrificed by cervical dislocation after general anesthesia. Liver was dissected out on ice quickly, cleaned and stored at -80^{o}C till the preparation for analysis. Liver homogenized in phosphate buffer slain 7.4 pH using a homogenizer surrounded with an ice jacket and the homogenates were used for the determination of the oxidative stress marker (MDA, GSH, GSSG, NO and 8-OH-dG) by HPLC.
Biochemical analysis Biochemical analyses of blood and 10% of homogenate liver were assayed according to the methods mentioned in table 1.

Statistical analysis

The values were expressed as the mean ± SE for the 10 rats in each group. Differences between groups were assessed by one way analysis of variance (ANOVA) using SAS (2004) [23] software for Windows (version 13.0). Statistical analysis of the obtained data was performed using the general linear model (GLM). Significant differences among means were evaluated using Duncan's (1955) **[24].** Multiple Range Test.
The following linear model was applied:
$Yij = \mu + \alpha i + \xi ij$
Yij = Observation measured
M = Overallmean
αi = Effect of treatment .
ξij = Experimental error assumed to be randomly distributed ($\sigma 2 = 0$).

Table 2: Methods and kits used to quantify the different biochemical analyses of blood and liver homogenate:

Parameters	Method	Company	Reference
AST	Enzymatic-colorimetric	Quimica Clinica Aplicada S.A.(Amposta, Spain)	**[25]**
ALT	Enzymatic-colorimetric	Quimica Clinica Aplicada S.A.(Amposta, Spain)	**[25]**
Total Lipids (g/dl)	Colorimetric	Biodiagnostic (Egypt)	**[26]**
Cholesterol (mg/dl)	Colorimetric	Stanbio Laboratory (Boerne, Texas,78202 USA)	**[27]**
Triglycerides (g/dl)	Colorimetric	Stanbio Laboratory(Boerne,	**[28]**

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		Texas,78202 USA)	
HDL	Colorimetric	Stanbio Laboratory (Boerne, Texas,78202 USA)	**[27]**
LDL	= TC-(TG/5)-HDL		
MDA (nmol/g tissue)	HPLC	Standard of 1, 1, 3, 3 tetraethoxypropane (Sigma)	**[29]**
GSH & GSSG	HPLC	Standard of 1, 1, 3, 3 tetraethoxypropane (Sigma)	**[30]**
NO (nmol/g tissue)	HPLC	Standard of nitite and nitrate (Sigma).	**[31]**
8-OH-dG (nmol/g tissue)	HPLC	Standard of 8 -hydroxy-2 – deoxyguanosine (Sigma).	**[32]**
TNF-α	ELISA	RayBio ® Rat TNF- α USA	**[33]**
IL-1β	ELISA	RayBio ® Rat IL-1 beta USA	**[33]**
IL-6	ELISA	RayBio ® Rat IL-6 USA	**[33]**

Results

Table 3: Effect of AJ, PM, PG, SO and herbal mixture once daily for 28 days after 60 days HFD on serum ALT and AST of male albino rats:

Groups	Parameters	
	ALT	**AST**
Control	38.46 ± 1.32^{e}	81.73 ± 2.82^{c}
HFD	101.03 ± 1.72^{a}	165.33 ± 2.8^{a}
AJ	78.54 ± 3.12^{b}	95.88 ± 3.81^{b}
PG	80.08 ± 4.46^{b}	95.20 ± 5.30^{b}
SO	66.20 ± 3.21^{c}	100.51 ± 4.88^{b}
PM	65.21 ± 2.31^{c}	101.49 ± 3.59^{b}
AJ+PM++PG+SO	47.74 ± 2.17^{d}	93.68 ± 4.26^{b}

a, b, c, d, e means having different superscript letters in the same column differ significantly ($P<0.05$).
As shown in Table 3, serum ALT and AST levels were significantly increased ($P<0.05$) following administration of HFD compared to the control group. However, treatment significantly showed enhancement in the recorded liver function markers compared to HFD group.

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Table 4: Effect of AJ, PM, PG, SO and herbal mixture once daily for 28 days after 60 days HFD on serum MDA, GSH, GSSG and NO of male albino rats:

Groups	Parameters				
	MDA	GSH	GSSG	NO	8-OH-dG
Control	11.82 ± 0.40^{d}	15.76 ± 0.54^{a}	0.612 ± 0.021^{e}	0.309 ± 0.011^{f}	298 ± 2.89^{d}
HFD	28.75 ± 0.49^{a}	11.02 ± 0.18^{d}	3.24 ± 0.055^{a}	2.054 ± 0.035^{a}	423 ± 6.31^{a}
AJ	18.63 ± 0.74^{b}	12.56 ± 0.50^{cd}	1.72 ± 0.068^{b}	1.373 ± 0.055^{bc}	372 ± 5.46^{b}
PG	16.35 ± 0.91^{c}	13.79 ± 0.76^{bc}	1.53 ± 0.085^{c}	1.474 ± 0.082^{b}	379 ± 8.02^{b}
SO	18.03 ± 0.87^{bc}	15.13 ± 0.73^{ab}	1.82 ± 0.088^{b}	1.162 ± 0.056^{d}	382 ± 8.27^{b}
PM	12.08 ± 0.42^{d}	15.038 ± 0.53^{ab}	1.91 ± 0.068^{b}	1.243 ± 0.044^{cd}	370 ± 7.87^{b}
AJ+PM++PG+SO	13.65 ± 0.62^{d}	14.10 ± 0.64^{abc}	0.806 ± 0.037^{d}	0.677 ± 0.031^{e}	358 ± 4.79^{c}

a, b, c, d, e, f means having different superscript letters in the same column differ significantly (P<0.05).

As shown in Table 6, serum MDA, GSSG and NO levels were significantly increased and decrease in GSH level (P<0.05) following administration of HFD compared to the control group. However, treatment significantly showed enhancement in the recorded liver oxidative stress markers compared to HFD group.

Table 5: Effect of AJ, PM, PG, SO and herbal mixture once daily for 28 days after 60 days HFD on serum TL, T.Ch, TG, HDL and LDL of male albino rats:

Groups	Parameters				
	TL	TCh	TG	HDL	LDL
Control	394 ± 13.6^{c}	98 ± 3.3^{b}	84 ± 2.9^{c}	39 ± 1.3^{a}	41 ± 1.4^{c}
HFD	702 ± 11.9^{a}	183 ± 3.1^{a}	195 ± 3.3^{a}	25 ± 0.4^{d}	119 ± 2.0^{a}
AJ	458 ± 18.2^{b}	106 ± 4.2^{b}	109 ± 4.3^{b}	32 ± 1.2^{bc}	52 ± 2.0^{b}
PG	472 ± 26.3^{b}	96 ± 5.39^{b}	107 ± 5.9^{b}	30 ± 1.6^{c}	44 ± 2.5^{c}
SO	483 ± 23.4^{b}	99 ± 4.8^{b}	108 ± 5.2^{b}	34 ± 1.6^{b}	42 ± 2.0^{c}
PM	508 ± 18.0^{b}	104 ± 3.7^{b}	103 ± 3.6^{b}	30 ± 1.0^{c}	53 ± 1.8^{b}
AJ+PM++PG+SO	401 ± 18.2^{c}	103 ± 4.7^{b}	101 ± 4.6^{b}	35 ± 1.6^{ab}	47 ± 2.1^{bc}

a, b, c. means having different superscript letters in the same column differ significantly (P<0.05).

As shown in Table 4, serum TL, T.Ch, TG and LDL levels were significantly increased and decrease in HDL level (P<0.05) following administration of HFD compared to the control group. However, treatment significantly showed enhancement in the recorded of lipid profile markers compared to HFD group.

Table 6: Effect of AJ, PM, PG, SO and herbal mixture once daily for 28 days after 60 days HFD on serum TNFά, IL-1β and IL-6 of male albino rats:

Groups	Parameters		
	TNFÜ	IL-1â	IL-6
Control	79.46 ± 2.74^{d}	42.65 ± 1.47^{c}	9.51 ± 0.32^{e}
HFD	135.08 ± 2.30^{a}	85.16 ± 1.45^{a}	40.41 ± 0.68^{a}
AJ	91.97 ± 3.65^{c}	50.79 ± 2.02^{b}	17.12 ± 0.68^{b}
PG	89.59 ± 4.99^{cd}	53.71 ± 2.99^{b}	14.98 ± 0.83^{cd}
SO	87.65 ± 4.25^{cd}	55.60 ± 2.70^{b}	15.90 ± 0.77^{bc}
PM	102.78 ± 3.64^{b}	54.71 ± 1.93^{b}	13.49 ± 0.47^{d}
AJ+PM++PG+SO	81.31 ± 3.70^{cd}	42.54 ± 1.93^{c}	10.51 ± 0.47^{e}

a, b, c,d,e. means having different superscript letters in the same column differ significantly (P<0.05).

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As shown in Table 5, serum TNFά, IL-1β and IL-6 levels were significantly increased (P<0.05) following administration of HFD compared to the control group. However, treatment significantly showed regulation in the recorded of inflammatory mediators compared to HFD group.

Discussion

Hyperlipidemia is one of the major modifiable risk factors for stroke. The American Heart Association states that treatment of hyperlipidemia reduces risk of stroke by 30% **[34].** Excessive quantities or improper types of lipid-intake may result in hyperlipidemia which is characterized by an abnormal elevation in one or more of the serum lipids such as total cholesterol (TC), low-density lipoproteincholesterol (LDL-C) and triglycerides (TG). The results showed that oxidative stress induced by hyperlipidemic diet in rats was characterized by retardation in body weight gain, an increase in lipid peroxidation and elevation in serum and liver biochemical markers of oxidative stress. These findings were partially similar to those obtained by **Young *et al*. (1995) [35]** who reported that B.wt, lipid profile oxidative stress marker and inflammatory mediators were greatly increased, while HDL and GSH were significantly decreased after 60 days high fat diet treated rats when compared to the untreated control group.

The results are summarized in Table 3 and 4. As shown, AJ decreased hepatic contents of ALT and AST, MDA, GSSG, NO and 8-OH-dG and increased their GSH contents as compared to HFD group. The major bioactive compounds of defatted alcoholic and water extracts of *Artemisia judaica* essential oils (artemisyl-oil, apiperitone-oil, piperitone and trans-ethyl cinnamate), saponins, terpenes, tannins, and flavinoids (apigenin, cirsimaritin, flavonoid glycosides) which have antioxidant, anti-inflammation and anti-hyperlipidemic activity **[36].** Supplementation of antioxidants may be a protective factor against free radical induced cell damage **[37].** Antioxidant activity of AJ may be due to a significant level of phenolic compounds including luteolin, luteolin-7-glucoside, kaempferol, quercetin, rutin, coumarin and so on **[38].** The co-effectiveness of *Artemisia* on hyperlipidemia and oxidative stress indicates a strong point of this medicinal plant. Oxidative stress is an early event in the evolution of hyperlipidemia, and affects the development of arteriosclerosis and myocardial infarction **[39].** AJ decreased lipid profile after 60 days of rats fed HFD, indicating improvement of TL, TC, TG, LDL and HDL. In agreement with the study of **Jang *et al*., (2012) [40],** they evaluated an antioxidant and lipid-lowering effects of *artemisia capillaris* on a Rat Model of Hyperlipidemia. Anti-hyperlipidemic effect of AJ may be due to improve lipid metabolism, body weight gain and adiposity and that peroxisome proliferator-activated receptor-γ (PPAR-γ) is associated with these events **[41].** AJ showed a significant decrease in TNF-α, IL-1β, and IL-6 production. This further proves that AJ regulates the inflammation by a significant decrease of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 by macrophages, which mediates many crucial events for the initiation of acute, sub acute and chronic inflammation. Also, it is having an anti-proliferative activity and the potential to directly react with free radicals **[42].** Recently**, Helal *et al*. (2015) [43]** showed that *Artemisia judaica* has a hepatoprotective effect and improving liver function. This may be due to the presence of flavonoids which have a hypoglycemic action in addition to a potent antioxidant action attenuating the oxidative stress induced by free radicals, so they can ameliorate the functions of the liver by protecting the hepatocytes and inhibiting the production proinflammatory mediators like TNF-α, IL-12, IL-2 cytokines which has been associated with inflammatory diseases**.**

Results of the current study revealed that oral administration of *Panax ginseng* (PG) to rats with oxidative stress induce by HFD improved liver function, reduced lipid peroxidation and decrease inflammatory mediators. PG was found to possess bioactive constituents which produce high antioxidant activity and prevent oxidation of lipids. Various phenolic compounds such as flavonoids, phenolic acids, diterpenes, saponins and tannins possess diverse biological activities and are thought to be beneficial for reducing cell damage induced by oxidative stress. The activity of phenolic compounds might be related to their antioxidant effect due to their ability to scavenge the free radicals by presence of hydroxyl groups in these compounds **[44].** The hepatoprotective action of PG reported in the present study was similar to that obtained by **[45].** Hypolipidemic effects of PG

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were in accordance with those reported by **Kawak *et al*. (2010) and Shin *et al*. (2011) [46, 47].** The antioxidant effect of PG, reported herein, agreed with that previously reported by **Lee *et al*. (2005) [45].** Also, areduction in serum triglycerides level was observed after treatment. These results were in agreement with the results of **[48].** who mentioned that ginseng markedly reduced serum triglycerides and cholesterol in hyperlipidemic monkeys. In addition, **Hwang *et al*. (2008) [49]** indicated that the administration of ginseng saponins to rabbits fed high cholesterol diet decreased the serum cholesterol level. In the current study hypolipidemic effect of PG may be due to saponins that, the natural appetite suppressants. Ginsam increases PPAR- γ expression and AMP-activated protein kinase phosphorylation in liver and muscle. The extracts strongly activate hormone specific lipase via protein kinase A. Saponin reduce the absorption of cholesterol and thus increase faecal excretion of cholesterol **[50].** The inhibitory effect of PG on hyperlipidemia may be due to inhibition of pancreaticlipase secretion was mainly due to the characteristic structure of saponin. Beyond lipase inhibition, other pathways mediating the effect were also involved. Two essential factors are noted here: one is the suppression of the food intake with high correlation to the body weight loss; the other is the regulation of the cholesterol metabolism with the resultant improvement of the lipoprotein composition and the hepatic lipid-lowering effect **[51].** In the current study, it was found that PG improved antioxidants' levels and decreased MDA, GSSG, NO and 8-OH-dG levels in the treated group when compared to the HFD group. In agreement, **Liu *et al*. (2003) [52]** found that ginseng extracts scavenge oxidative species; also, **Surh *et al*. (2001) [53]** indicated that ginseng extracts attenuate lipid peroxidation. That is, it may be related to saponins which play a major role in antioxidant activities. In addition, ginsenoides which are important components heavily present in ginseng production of powerful antioxidant activities other than radical scavenging activities by stimulating gene expression of antioxidant enzymes and enhancing their activities **[54].** In the present study, the mean values of serum TNF-α, IL-1β and IL-6 were increased in the HFD group and then improved by ginseng treatment. These results were in agreement with **Kim *et al*. (2003) [55]** who reported that, ginseng saponins have been proposed as possible candidates in the research of therapeutic modulation of stress-related disorders, for their inhibitory effect on the level of stress induced IL-6 in mice. Moreover, **Chun *et al*. (2007) [56]** indicated that ginsenoides inhibited the lipopolysaccharide induced production of TNF-α by blocking transcription factor (NF - KB) which regulates the transcription of many gene associated with inflammation.

Salvia officinalis (SO) showed hepato-protective effect by decreasing activities of ALT and AST after 60 days HFD. **Bassil *et al*. (2015) [57]** revealed that SO could significantly decrease the levels of ALT and AST ($P < 0.05$) in serum of HFD rats. Treatment with SO extract strongly decrease the level of lipid peroxidation compared to HFD rats, which may be due to its free radical scavenging potential induced by HFD. It is known that SO has inhibitory effect in lipid peroxidation induced by Fe^{+2} and Cu^{+2} by its free radical scavenging potential **[58].** Because of central role of transition metals in lipid peroxidation process, our observations confirm the ability of SO to scavenging free radicals and inhibition of lipid peroxidation damage in HFD model. Ethanolic extract of SO had a potent increasing effect on GSH level decreasing MDA, GSSG, NO and 8-OH-dG on liver tissues compared to HFD rats. Antioxidant activity of SO may be due to phenolic and flavonoid compounds are mainly responsible for the antioxidant and free radical scavenging effect. Antioxidant activity of SO was similar with **Nickavar, 2007; Yadav and Mukundan 2011 [59, 60]**. Phenolic compounds such as carnosol, carnosic and rosmarinic acids have a high antioxidative activity and are usually extracted from SO with ethanol **[61].** The phenolic compounds can either stimulate endogenous antioxidant defense systems or scavenge reactive species **[62].** The similar results in another study confirmed that SO could decrease the oxidative stress marker and increase GSH in trichloroacetic acid induced increased serum marker enzymes lipid peroxidation antioxidative defense systems in rats **[63].** Concerning the anti-obesity properties of SO, the results presented here demonstrate that the lipid profile of HFD rats treated with SO showed neutralization of TC, TG, LDL and HDL. Anti-obesity of SO may be due to pancreatic lipase inhibitor of

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carnosic acid, Carnosic acid also significantly inhibited triglyceride elevation in olive oil-loaded mice and reduced the gain of body weight and the accumulation of epididymal fat weight in high fat diet-fed mice after 14 days **[64].** Pancreatic lipase is well known to play an important role in lipid digestion **[65].** The ethanolic extract from the leaves of Salvia officinalis. Significantly inhibited the pancreatic lipase activity, and suppressed serum triglyceride (TG) elevation in olive oil-loaded mice **[64].** These results are compatible with **Christensen, (2010) [66]** who concluded that SO improved HDL and decreased lipid profile rat serum fed HFD. Therapeutic effect of SO significantly inhibited cytokine production (TNF-α, IL-1β and IL-6) in serum rat fed HFD. *Polygonum multifurum* **(**PM) (Polyphenolic compounds) have an important role in stabilizing lipid oxidation and are associated with antioxidant activity by lowering ALT, AST, MDA, GSSG, NO and 8-OH-dG. These results suggest that PM not only inhibits the hepatic local inflammatory response, but also attenuates the positive feedback loop between oxidative stress and inflammation. The obtained results confirmed with **Abd El-Kader *et al*. (2012) and Zhang, *et al*. (2012) [67,68]** for antioxidant and hepatoprotective activity of the plant who suggested that polygonum stabilizing level of liver function, oxidative stress markers and inflammatory mediators. In present study, PM group can significantly reduce the TL, TC, TG and LDL in hyperlipidemic rats. This may be due to the phenolic hydroxyls contained in phenolic compounds, through oxidation. Cholesterol is suppressed and unsaturated fatty acids are oxidized. The obtained results confirmed with **Xie, *et al*. (2014) [69]** for the lowering effect of flavonoids (resveratrol) on lipid metabolism in hyperlipidemic mice.

The present results also showed that the antioxidant, anti-obesity and anti-inflammatory effects of herbal cocktail was amplified by its co-administration with AJ 50mg/kg B.wt, PG 50mg/kg B.wt, SO 100 mg/kg B.wt and PM 400 mg/kg B.wt after rats fed 60 days HFD.

Our study demonstrated that herbal cocktail (mixture of AJ 50mg/kg B.wt, PG 50mg/kg B.wt, SO 100 mg/kg B.wt and PM 400 mg/kg B.wt) after rats fed 60 days HFD could increase antioxidant capacity, decrease oxidative stress markers, decrease hyperlipidemia and inflammatory mediators. Antihyperlipidemia of herbal cocktail may be due to natural lipid metabolism regulators of AJ, natural appetite suppressants of PG (saponin), natural pancreatic lipase inhibitors of SO (Carnosic acid) and suppresses the elevated mRNA expression levels of sterol regulatory element-binding protein-1c, peroxisome PPAR-γ, fatty acid synthase, and adipocyte protein 2 in the white adipose tissue of PM.

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