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Influence of Ginseng, Curcumin and Their Combination on Rats Suffering from Diabetes and Acute Liver Diseases

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Abstract: This study was carried out to determine the effect of two levels from ginseng and curcumin and their combination on nutritional evaluation, kidney functions, lipid profile and liver enzymes of diabetic rats suffering from acute liver diseases. Forty-eight male albino rats (Sprague Dawley Strain) weighting an average of (150±5g) used in this study. The rats were divided into two main groups. The first main group (6 rats) was fed on basal diet as a (control negative group). The second main group (42 rats) treated with CCl_4, in paraffin oil (50% v/v 4 ml/kg) subcutaneous injection to induced acute damage in the liver. The second main group injected with (150mg alloxan/kg body weight) to induce hyperglycemia. The second main group was divided into seven subgroups (6 rats each). The first subgroup fed on basal diet as a control positive group. The second and third subgroups fed on basal diet containing 2% and 4% ginseng, respectively. The fourth and fifth subgroups fed on basal diet containing 0.25% and 0.5% curcumin, respectively. The sixth subgroup fed on basal diet containing (2% ginseng and 0.25% curcumin). The seventh subgroup fed on basal diet containing (4% ginseng and 0. 5% curcumin). The results revealed that, feed intake, body weight gain% and serum HDL-c decreased, while other parameters increased in the positive control group, as compared to the negative control group. Treating diabetic groups which were suffering from acute liver disease with 2% and 4% ginseng, 0.25% and 0.5% curcumin and their combination improved the weight gains, organs weight/body weight%, kidney functions (uric acid, urea nitrogen and creatinine), lipid profile (cholesterol, triglycerides, HDL-c, LDL-c and VLDL-c) and liver enzymes (AST, ALT and ALP), especially the groups which were treated with the high and low levels from the combination of (4% ginseng and 0.5% curcumin) and (2% ginseng and 0.25% curcumin), respectively.

Key words: Acute liver diseases · Curcumin · Diabetes · Ginseng · Kidney functions · Lipid profile · Liver enzymes

INTRODUCTION

Diabetes mellitus is one of the major global public health problems. Recently, a survey estimated that there will be more than 439 million people suffering from diabetes in nearly all countries by the year 2030 [1]. Type 2 diabetes is a complex, heterogenous, polygenic disease characterized mainly by insulin resistance and pancreatic b-cell dysfunction [2], many patients who suffer from T2DM are at an increased risk of developing further complications over time. Increasing evidence is now linking T2DM with liver disease especially acute liver failure (ALF); it is a complex multisystemic illness that evolves after a catastrophic insult to the liver manifesting in the development of a coagulopathy and encephalopathy within a short period of time [3]. Type 2 diabetes is associated with a large number of liver disorders, Up to 96% of patients with cirrhosis have diabetes or impaired glucose intolerance in one report – and this diabetes is different from type 2 diabetes because it occurs in the absence of standard risk factors of type 2 diabetes such as age, body mass index and family history of diabetes [4, 5]. Nowadays the management of diabetes in patients with liver disease is theoretically complicated by first; accompany with considerable side effects of drugs such as hypoglycemia,

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drug-resistance, dropsy and weight gain [1]**;** second; liver-related alterations in drug metabolism, potential interactions between the drugs and incidence of hepatotoxicity [6]. Thus, there is an increasing demand on searching for the antidiabetic agents from natural resource with fewer side effects, for example, looking for the active components from the traditional medicine [7]. One of the promising medicinal plants with anti-diabetic potential is ginseng; Panax ginseng has been used in China for thousands of years as herbal medicine that is known to exert the beneficial effect, such as anti-fatigue, anti-obesity, anti-cancer and antioxidant [8]. Studies by Luo and Luo [9] have revealed American ginseng's ability to decrease blood glucose in type II diabetes patients as well as in STZ-diabetic mice, These data suggested that effects of ginseng in improving hyperglycemia may alter mitochondrial function as well as apoptosis cascades to ensure cell viability in pancreatic islet cells. Vuksan *et al.* [10] demonstrated that 3g American Ginseng (AG; *Panax quinquefolius* L.) given 40 minutes before a 25g glucose challenge improves postprandial glucose tolerance in individuals with and without type 2 diabetes by approximately 20%. Another basic action of ginseng extract is to increase non-specific resistance of the organism and stimulates various metabolic reactions in the liver cells [11]. Ginsenosides are the bioactive components found mainly in the roots of ginseng. Structurally, ginsenosides are divided into two types: protopanaxadiol ginsenosides (PPDGs) and protopanaxatriol ginsenosides (PPTGs) [12]. There are two major classes of ginsenosides, the derivatives of protopanaxatriol and protopanaxadiol which are mainly found in organic extract while the aqueous extract contains polysaccharides predominantly. In the context of diabetic complications, it is possible that ginseng through its antioxidant effects, may prevent glucose-induced damage [13]. Turmeric is another spice, used as a traditional medicine plant in India for treating various diseases. Curcuma is derived from the root of the Curcuma Longa plant first by drying and powdering, to create the spice called Turmeric [14]. Turmeric is an excellent liver herb, it is used for jaundice and to stimulate gallbladder activity, increase detoxifying enzymes [15], helpful as a digestive aid for breaking down and digesting fatty foods, reduces the oxidation of LDL, blood glucose and renal lesions in diabetes [16]. Turmeric has shown anti-inflammatory, anti-oxidant, antifungal, antibacterial and anticancer activities [17]. The active ingredients of curcumin are curcuminoids; it is polyphenolic compounds with a β-diketonemoiety. The three types of curcuminoids, namely Curcumin I, II and III, differ with regard to their hydroxyl and methyl groups, characteristic with yellow color [18]. Various animal models [19, 20] or human studies [21, 22] proved that curcumin is extremely safe even at very high doses. In the present study we have investigated the effect of ginseng, curcumin and their combination on rats suffering from diabetes and acute liver failure.

MATERIALS AND METHODS

- Carbon tetrachloride (CCl_4), alloxan, casein, vitamins, minerals, cellulose and choline chloride were purchased from El-Gomhouria Company, Cairo Egypt.
- Forty-eight male albino rats (Sprague Dawley Strain) were obtained from Helwan farm.
- Ginseng and Curcumin were purchased from local market, A.R.C. Cairo, Egypt.

The Biological Assay: Male rats (150±5g) were kept in individual stainless steel cages under hygienic conditions and fed one week on basal diet for adaptation in *ad libitum*. The basal diet in the preliminary experiment consists of 14% casein (protein > 80%), corn oil 4%, cellulose 5%, vitamin mixture 1%, salt mixture 3.5%, choline chloride 0.25% and the remainder is corn starch [23]. Vitamin composition of the diets prepared according to A.O.A.C. [24]. After a period of adaptation on basal diet (one week), the rats were divided into two main groups. The first main groups (6 rats) fed on basal diet as a negative control group, the second main group (42 rats) treated with CCl_4, in paraffin oil (50% v/v 4 ml/kg) subcutaneous injection to induced acute damage in the liver [25]. The second main group injected with (150mg alloxan/kg body weight) to induce hyperglycemia according to the method described by [26].The second main group was divided into seven subgroups (6 rats each). The first subgroup fed on basal diet as a control positive group. The second and third subgroups fed on basal diet containing 2% and 4% ginseng, respectively. The fourth and fifth subgroups fed on basal diet containing 0.25% and 0.5% curcumin, respectively. The sixth subgroup fed on basal diet containing (2% ginseng and 0.25% curcumin). The seventh subgroup fed on basal diet containing (4% ginseng and 0. 5% curcumin).

During the experimental period (28 days), the diets consumed and body weights were recorded twice weekly. At the end of the experiment, the animals were fasted overnight, then the rats were anaesthetized and

sacrificed and blood samples were collected from the aorta. The blood samples were centrifuged and serum was separated to estimate some biochemical parameters, i.e. uric acid [27], urea nitrogen [28], creatinine [29], serum cholesterol [30], triglycerids [31], HDL-c [32], LDL-c and VLDL-c [33], serum glucose [34], aspartate amino transferase (AST) and alanine amino transferase (ALT) [35] and alkaline phosphatase (ALP) was determined according to the method described by Kind and King [36]. Liver and kidney were separated from each rat and weighted to calculate organs to body weight%.

Statistical Analysis: The obtained data was analyzed statistically for standard deviation and one way ANOVA test [37].

RESULTS

Feed Intake: Data presented in Table 1 showed the effect of two levels from ginseng, curcumin and their combination on feed intake of rats suffering from diabetes and acute liver diseases, the results indicated to a significant decrease $p< 0.05$ in feed intake in rat groups as compared to the negative control group NC, except that two groups which feeding on 4% ginseng and 0.25% curcumin.

Body Weight Gain%: The results of this table showed non-significant changes of the initial weight between all groups, after the end of trail period, the final weight decreased significantly in all treated groups compared to NC group, but still increased significantly compared to the positive control group PC. Body weight gain% (BWG%) showed a significant decreased in all tested groups, compared to the NC. On the other hand, all tested groups recorded significant increase $p<0.05$ in BWG%, as compared to the PC. The highest increase in BWG% recorded for the group which treated with 4% ginseng + 0.5% curcumin followed by the groups treated with 4% ginseng, 2% ginseng + 0.25% curcumin and 0.5% curcumin, respectively.

Organs Weight/body Weight%: Data in Table 1 revealed that weight of kidney and liver as a percent of body weight were changed, statistical analysis showed a significant increase $p< 0.05$ in kidney and liver weight/body weight% for PC group compared to NC group. Addition of ginseng and curcumin to the diet decreased the mean values of kidney and liver weight/body weight% significantly at $p<0.05$ in rats suffering from diabetes and acute liver failure, as compared to PC group. Treating rats which suffering from diabetes and acute liver diseases with the two levels of ginseng (2% and 4%), curcumin (0.25% and 0.5%) and their combination led to significant improvement in liver and kidney weights/body weights%, except group of rats which treated with 0.25% curcumin and the group treated with 2% ginseng, as compared to the PC. The highest improvement in liver and kidney weights/body weights% recorded for the group which treated with 4% ginseng + 0.5% curcumin, because this treatment showed significant decrease $p<0.05$, as compared to other treated groups.

Data presented in Table 2 illustrated that, the mean values of serum uric acid, urea nitrogen and creatinine (mg/dl) for PC group showed a significant increase at $p<0.05$, compared to NC group. All groups fed on basal diet containing ginseng, curcumin and their combination showed a significant reduction $p <0.05$ in mean values of uric acid, urea nitrogen and creatinine at $p<0.05$, compared with PC group. The mean values of serum uric acid, urea

Table 1: Effect of two levels from ginseng, curcumin and their combination on feed intake, weights and some organs weight / body weight% of rats suffering from diabetes and acute liver diseases.

Parameters	Feed intake	Initial weight	Final weight	Body	Organs weight / body weight%	
Groups	g/day/rat	G		weight gain%	Liver	Kidney
Control (-ve) (NC)	16.833 ^{a}± 0.983	149.500 ^{a}± 3.619	215.000 ^{a}± 4.472	43.833 ^{a}± 2.065	2.406 ^{a}± 0.108	0.437 ^{d}± 0.041
Control (+ve) (PC)	14.833 ^{b}± 0.752	150.000 ^{a}± 3.405	124.166 ^{e}± 3.600	-17.203 ^{f}± 2.414	4.202 ^{a}± 0.123	0.788 ^{a}± 0.029
2% ginseng	15.329 ^{b}± 0.408	150.166 ^{a}± 3.970	142.833 ^{d}± 4.578	-4.311 ^{d}± 3.920	4.061 ^{b}± 0.084	0.761 ^{a}± 0.027
4% ginseng	15.830 $^{a b}$± 0.683	151.500 ^{a}± 3.781	162.500 ^{c}± 7.395	7.225 ^{c}± 2.814	3.777 ^{d}± 0.078	0.701 ^{b}± 0.025
0.25% curcumin	15.916 $^{a b}$± 0.801	151.667 ^{a}± 3.141	137.333 ^{d}± 4.633	-9.467 ^{e}± 1.442	4.155 $^{a b}$± 0.131	0.764 ^{a}± 0.018
0.5% curcumin	15.433 ^{b}± 0.864	151.833 ^{a}± 1.602	158.330 ^{c}± 4.131	4.274 ^{c}± 2.149	3.893 ^{c}± 0.066	0.729 ^{b}± 0.017
2% ginseng + 0.25% curcumin	15.166 ^{b}± 0.816	152.000 ^{a}± 3.033	162.500 ^{c}± 5.357	6.889 ^{c}± 1.874	3.625 ^{c}± 0.098	0.698 ^{b}± 0.025
4% ginseng + 0.5% curcumin	15.083 ^{b}± 1.068	151.166 ^{a}± 1.169	169.166 ^{b}± 3.430	11.907 ^{b}± 2.138	3.464 ^{f}± 0.065	0.635 ^{c}± 0.024

- Values are expressed as mean ± SD.
- Significant at $p<0.05$ using one way ANOVA test.
- Values which have different letters in each column differ significantly, while those with have similar or partially are not significant.

Table 2: Effect of two levels from ginseng, curcumin and their combination on kidney functions of rats suffering from diabetes and acute liver diseases.

Parameters	Uric Acid	Urea Nitrogen	Creatinine
Groups	----------mg/dl----------		
Control (-ve) (NC)	1.319 ^{g}± 0.054	25.741 ^{f}± 1.648	0.498 ^{g}± 0.062
Control (+ve) (PC)	2.751 ^{a}± 0.118	67.112 ^{a}± 3.812	1.862 ^{a}± 0.077
2% ginseng	2.356 ^{c}± 0.091	57.833 ^{b}± 4.711	1.545 ^{c}± 0.102
4% ginseng	2.025 ^{e}± 0.083	47.344 ^{c}± 2.811	1.222 ^{e}± 0.091
0.25% curcumin	2.496 ^{b}± 0.073	60.241 ^{b}± 3.241	1.655 ^{b}± 0.069
0.5% curcumin	2.220 ^{d}± 0.055	50.515 ^{c}± 2.548	1.359 ^{d}± 0.071
2% ginseng + 0.25% curcumin	2.015 ^{e}± 0.124	42.207 ^{d}± 2.296	1.177 ^{e}± 0.069
4% ginseng + 0.5% curcumin	1.643 ^{f}± 0.087	35.495 ^{e}± 2.458	0.826 ^{f}± 0.088

- Values are expressed as mean ± SD.
- Significant at p<0.05 using one way ANOVA test.
- Values which have different letters in each column differ significantly, while those with have similar or partially are not significant.

Table 3: Effect of two levels from ginseng, curcumin and their combination on lipid profile of rats suffering from diabetes and acute liver disease

Parameters	Cholesterol	Tg	HDL-c	LDL-c	VLDL-c	LDL-c / HDL-c	TC/ HDL-c
Groups	----------mg/dl----------						
Control (-ve) (NC)	76.440 ^{f}± 4.005	45.678 ^{c}± 3.151	47.790 ^{a}± 3.109	19.214 ^{h}± 1.142	9.435 ^{c}± 0.942	0.402 ± 0.027 ^{g}	1.600 ± 0.034 ^{g}
Control (+ve) (PC)	192.941 ^{a}± 6.220	97.417 ^{a}± 4.940	20.805 ^{c}± 2.899	152.652 ^{a}± 3.215	19.483 ^{a}± 0.988	7.460 ± 1.082 ^{a}	9.409 ± 1.190 ^{a}
2% ginseng	175.940 ^{b}± 4.676	84.226 ^{b}± 5.688	26.419 ^{d}± 2.881	132.675 ^{c}± 0.984	16.845 ^{b}± 1.137	5.072 ± 0.561 ^{c}	6.712 ± 0.598 ^{c}
4% ginseng	157.480 ^{c,d}± 4.519	69.140 ^{c}± 4.612	32.968 ^{c}± 2.305	110.684 ^{e}± 1.632	13.827 ^{c}± 0.922	3.368 ± 0.199 ^{e}	4.787 ± 0.206 ^{e}
0.25% curcumin	179.656 ^{b}± 3.910	85.281 ^{b}± 3.221	23.290 ^{c}± 1.441	139.310 ^{b}± 1.896	17.056 ^{b}± 0.644	5.996 ± 0.294 ^{b}	7.729 ± 0.314 ^{b}
0.5% curcumin	162.941 ^{c}± 4.463	71.846 ^{c}± 2.441	28.095 ^{d}± 1.529	120.477 ^{d}± 2.691	14.369 ^{c}± 0.488	4.294 ± 0.164 ^{d}	5.806 ± 0.175 ^{d}
2% ginseng + 0.25% curcumin	156.126 ^{d}± 5.764	70.649 ^{c}± 4.821	35.087 ^{c}± 3.600	106.914 ^{f}± 1.752	14.129 ^{c}± 0.964	3.071 ± 0.293 ^{e}	4.474 ± 0.308 ^{e}
4% ginseng + 0. 5% curcumin	125.035 ^{e}± 4.173	54.936 ^{d}± 3.889	39.311 ^{b}± 2.743	74.736 ^{g}± 1.245	10.987 ^{d}± 0.778	1.908 ± 0.122 ^{f}	3.187 ± 0.126 ^{f}

- Values are expressed as mean ± SD.
- Significant at p<0.05 using one way ANOVA test.
- Values which have different letters in each column differ significantly, while those with have similar or partially are not significant.

nitrogen and creatinine decreased gradually with increasing the levels of ginseng, curcumin and their combination. Feeding rats suffering from diabetes and acute liver disease on diet containing combination of 4% ginseng + 0.5% curcumin showed the higher reduction in kidney functions, as compared to all tested groups. This treatment decreased serum uric acid, urea nitrogen and creatinine by about 40.276%, 47.110% and 55.639%, than that of the positive control group, respectively.

The data presented in Table 3 indicated the effect of two levels from ginseng, curcumin and their combination on lipid profile of rats suffering from diabetes and acute liver failure. The mean values of serum cholesterol, triglycerides, low density lipoprotein-cholesterol LDL-c and very low density lipoprotein-cholesterol VLDL-c increased significantly at p<0.05, whereas the mean values of serum high density lipoprotein-cholesterol HDL-c decreased significantly p<0.05 in PC group compared to NC group. Injected rats with (Alloxane and CCL4) and received diets with two levels of ginseng, curcumin and their combination led to significant decrease p< 0.05 in serum (cholesterol, triglycerides, LDL-c and VLDL-c), while HDL-c increased significantly, as compared to the PC group. The best result of lipid profile was noticed in group of rats fed on basal diet containing a combination of 4% ginseng + 0.5% curcumin, followed by group that treated with a combination of 2% ginseng + 0.25% curcumin.

On important risk factors such as diabetes mellitus, the LDL-C/HDL-C ratio is often calculated to estimate CHD risk. As presented in the same table, LDL-C/HDL-C, TC/HDL-C ratios was calculated. These ratios significantly increased for PC group in comparison with NC group. Treating diabetes and acute liver failure rats with basal diet containing some levels of ginseng and curcumin and their combination had lower mean values in LDL-C/HDL-C and TC/HDL-C than that of PC group. On the other hand, the combination of ginseng and curcumin (with high level) showed significant decrease (P<0.05) in the mean values of LDL-C/HDL-C and TC/HDL-C, as compared to other treated groups.

The results in Table 4 revealed that, there was a significant increase in serum glucose (mg/dl) of PC group, as compared to NC group. Glucose of all treated groups with 2% & 4% of ginseng, 0.25% & 0.5% of curcumin and their combination recorded significant decrease p<0.05, as compared to PC group. Concerning of liver enzymes (Aspartate Amin tranferase AST, Alanine Amin transferase ALT and Alkaline Phosphatase ALP), results observed that rats which suffer from diabetic and acute

Table 4: Effect of two levels from ginseng, curcumin and their combination on serum glucose and liver enzymes of rats suffering from diabetes and acute liver disease

Parameters	Glucose mg/dl	AST	ALT	ALP
Groups	----------	----------μ/l----------	----------	----------
Control (-ve)	70.887 ^{f}± 4.002	59.719 ^{g}± 3.301	19.705 ^{h}± 1.943	81.050± 3.040
Control (+ve)	193.398 ^{a}± 5.101	149.125 ^{a}± 5.366	80.409 ^{a}± 4.415	178.386 ^{a}± 8.103
2% ginseng	170.705 ^{b}± 4.041	132.881 ^{b}± 3.669	71.338 ^{b}± 3.255	159.829 ^{b}± 4.666
4% ginseng	133.325 ^{d}± 4.155	108.737 ^{d}± 4.242	59.329 ^{d}± 3.197	139.688 ^{c}± 5.221
0.25% curcumin	173.507 ^{b}± 3.250	126.795 ^{c}± 3.218	66.296 ^{c}± 3.155	154.552 ^{b}± 5.051
0.5% curcumin	140.254 ^{c}± 5.138	98.565 ^{e}± 3.657	51.284 ^{e}± 3.454	119.324 ^{d}± 4.350
2% ginseng + 0.25% curcumin	132.241 ^{d}± 5.035	94.793 ^{e}± 2.889	46.678 ^{f}± 3.789	137.493 ^{c}± 4.798
4% ginseng + 0.5% curcumin	109.835 ^{e}± 4.308	75.110 ^{f}± 4.739	36.251 ^{g}± 3.542	100.403 ^{e}± 4.494

- Values are expressed as mean ± SD.
- Significant at $p<0.05$ using one way ANOVA test.
- Values which have different letters in each column differ significantly, while those with have similar or partially are not significant.

liver failure in PC group had higher mean values than that of NC group. Values of serum AST, ALT & ALP (μ/l) decreased gradually with increasing the level of ginseng, curcumin and their combination. Ratios of decreasing AST, ALT & ALP percent were about 49.6%, 54.9% & 43.7% respectively, when treated rats with combination of 4% ginseng + 0.5% curcumin compared with PC group.

DISCUSSION

There is definite evidence for an ominous association between diabetes mellitus and liver disease. An insulin-resistant state may be demonstrated in approximately 80% of patients with cirrhosis and 20-63% of them will develop diabetes mellitus (hepatogenous diabetes) [38]. It is well recognized that liver is one of the most important organs in the biotransformation of food, drugs, endogenous and exogenous substances. Profuse supply of blood and the presence of many redox systems (e.g. cytochromes and various enzymes) enable liver to convert these substances into different kinds of inactive, active or even toxic metabolites. The burden of metabolism and exposure to dangerous chemicals make liver vulnerable to a variety of disorders, such as acute or chronic inflammation, toxin-/drug-induced hepatitis, cirrhosis and hepatitis after viral infection [12]. In recent years many researchers have examined the effects of plants used traditionally by indigenous healers and herbalists to support liver function and treat diseases of the liver. In most cases, research has confirmed traditional experience and wisdom by discovering the mechanisms and modes of action of these plants as well as reaffirming the therapeutic effectiveness of certain plants or plant extracts in clinical studies. The current study demonstrated the efficacy of 2% & 4% of ginseng, 0.25% & 0.5% of curcumin and their combination at improving kidney functions, lipid profile, serum glucose and liver enzymes of rats suffering from diabetes and acute liver diseases.

Diabetic nephropathy is a major cause of morbidity in diabetic patients. A structural hallmark of this disease is thickening of the glomerular basement membrane and mesangial matrix expansion. Biochemically, such lesions are characterized by increased production of extracellular matrix (ECM) proteins [39]. These alterations, which are characteristic in the kidneys in diabetes, were prevented with curcumin. Furthermore, curcumin has been shown to prevent oxidative stress in several cell types including endothelial cells and in several malignant cell types [40]. In addition, previous studies showed that ginseng prevented enhanced albuminuria and alterations of serum creatinine levels as well as mesangial matrix expansion, well established markers of renal damage in diabetes [41]. Sena *et al.* [42] indicated that oral administration of ginseng to the diabetic animals prevented the renal function abnormalities. In our investigation, a combination of 4% ginseng + 0.5% curcumin showed the higher reduction in kidney function, compared to all tested groups which suffering from diabetes and acute liver disease.

Turmeric is fairly rich in omega-3 fatty acids, curcuminoids are polyphenolic compounds with a β-diketone moiety [15]. The antioxidant capacity, a measure of the total protective antioxidant mechanisms of curcumin has been considered to be mediated via its beneficial effects on the antioxidant defense system, the scavenging of free radicals and preventing lipid peroxidation and it is at least 10 times more active as an antioxidant than vitamin E [43, 44]. In addition, ginsenoides which are important components heavily present in ginseng production of powerful antioxidant activities other than r adical scavenging activities by

stimulating gene expression of antioxidant enzymes and enhancing their activities [45]. Several studies of Dixit *et al*. [46] and Hwang *et al*. [47] mentioned that ginseng markedly reduced serum triglycerides and cholesterol in hyperlipidemic monkeys, administration of ginseng saponins to rabbits fed high cholesterol diet decreased the serum cholesterol level. In addition oral administration of red ginseng powder reduced plasma total cholesterol, triglyceride, while plasma HDL cholesterol was elevated. Platelet adhesiveness was also reduced and plasma lipid improving in patients with hyperlipidemia. Hepatic cholesterol and triglyceride contents were decreased and phospholipids increased by ginseng administration in the high cholesterol diet-fed rats, corresponding to improvement of the fatty liver. Ginseng extract have been reported to demonstrate strong antioxidant activity as it quenches free radicals, protects low density lipoproteins from oxidation and inhibits lipid peroxidation [48]. These results were in agreement with the presented study which indicated that a reduction in serum cholesterol, triglycerides, LDL-c and VLDL-c level and increasing in serum HDL-c were observed in group of rats fed on basal diet containing a combination of 4% ginseng + 0.5% curcumin. In addition, the combination of the same high level of ginseng and curcumin showed a significant decrease in LDL-C/HDL-C, TC/HDL-C ratios. Curcumin is a potent scavenger of reactive oxygen and nitrogen species such as hydroxyl radicals and nitrogen dioxide radicals [40].

Farhangkhoee *et al.* [49] reported that curcumin is effective in preventing glucose-induced oxidative stress in the endothelial cells and in the heart of diabetic animals. Sharma *et al.* [50] has also been shown that short-term treatment of diabetic rats with curcumin prevents diabetes-induced decreased antioxidant enzyme levels and kidney dysfunction. Suryanarayana *et al.* [51] revealed that turmeric and curcumin appear to be beneficial in preventing diabetes-induced oxidative stress in rats despite unaltered hyperglycemic status.

American ginseng root displays the ability to achieve glucose homeostasis both experimentally and clinically but the unknown mechanism used by ginseng to achieve its therapeutic effects on diabetes limits its application. Disruption in the insulin secretion of pancreatic β cells is considered the major cause of diabetes. A mitochondrial protein, uncoupling protein-2 (UCP-2) has been found to play a critical role in insulin synthesis and β cell survival [52]. Previous studies have revealed that American ginseng lowers blood glucose in diabetic patients [10] and benefits pancreatic β cell insulin production, secretion and prevents β cell apoptosis [53]. Ginsenosides such as Rh2 also demonstrated glucose lowering effect in STZ-induced rats [54]. Both the saponin and polysaccharide constituents in ginseng are thought to be responsible for its observed hypoglycemic effects. Preliminary in vitro and animal studies have indicated that ginseng may promote insulin release, increase insulin receptors and enhance insulin sensitivity [55]. In the current study, it was found that curcumin and ginseng improved glucose homeostasis, a reduction observed after treated with 2% & 4% of ginseng, 0.25% & 0.5% of curcumin and their combination. Rivera-Espinoza and Muriel [17] found that oral administration of curcumin (30 mg/kg body weight) for 10 days lowered the liver and serum lipid peroxide levels, serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and lactate dehydrogenase (LDH), curcumin reduces the iron-induced hepatic damage by lowering lipid peroxidation. Turmeric may increase detoxification systems, the study evaluated the effects of turmeric on the liver's ability to detoxify xenobiotic (toxic) chemicals, levels of two very important liver detoxification enzymes (UDP glucuronyl transferase and glutathione-S-transferase) were significantly elevated in rats fed turmeric as compared to controls [56]. The mechanisms which provide ginseng's hepatoprotective effects are closely attributed to antioxidation properties. Ginseng enhanced the antioxidant defense mechanism [57] and increased self-antioxidant enzyme activities of superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, glutathione-S-transferase and heme oxygenase-1 in the aged-rat liver [58] and hepatotoxins-induced liver damages in rats [57, 59]. Ginseng treatments inhibited oxidative stress damage such as lipid peroxidation [58, 60], malondialdehyde, thiobarbituric acid reactive substance [57, 61], alanine aminotransferase, aspartate aminotransferase and lactate dehydrogenase [11, 62, 63]. Recently, further molecular mechanism studies found that ginseng suppresses mitogen-activated protein kinase signals [64]. Nuclear factor-kappa B and inducible nitric oxide synthase protein expression [61, 65]. In the present study, the level of serum liver enzymes (AST, ALT & ALP) were increased in the diabetic and acute liver disease group and then showed a significant decline gradually by curcumin and ginseng treatment.

CONCLUSION

This study has shown that Ginseng, Curcumin and their combination, improved glucose homeostasis, declined liver enzymes, prevented the renal function abnormalities, inhibited oxidative stress damage, which may help in the treatment of diabetes and acute liver diseases.

REFERENCES

1. Shaw, J.E., R.A. Sicree and P.Z. Zimmet, 2010. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Research and Clinical Practice, 87: 4-14.
2. Salas-Salvado, J., M.A. Martinez-Gonza, M. Bullo and E. Ros, 2011. Theroleofdiet in the prevention of type 2 diabetes. Nutrition Metabolism and Cardiovascular Diseases, 21: 32-48.
3. Grady, J., 2005. Acute liver failure. Postgrad. Med. J., 81: 148-154.
4. Hickman, I.J. and G.A. Macdonald, 2007. Impact of Diabetes on the Severity of Liver Disease. The American Journal of Medicine, 120: 829-834.
5. Holstein, A., S. Hinze, E. Thiessen, A. Plaschke and E.H. Egberts, 2002. Clinical implications of hepatogenous diabetes in liver cirrhosis. J. Gastroenterol Hepatol., 17: 677-681.
6. Tolman, K.G., V. Fonseca, A. Dalpiaz and M.H. Tan, 2007. Spectrum of liver disease in type 2 diabetes and management of patients with diabetes and liver disease. Diabetes Care. Mar., 30(3): 734-43.
7. Liu, Z., W. Li, X. Li, M. Zhang, L. Chen, Y.N. Zheng, G.Z. Sun and C.C. Ruan, 2013. Antidiabetic effects of malonyl ginsenosides from Panax ginseng on type 2 diabetic rats induced by high-fat diet and streptozotocin. J. Ethnopharmacol., 145(1): 233-40.
8. Liu, Z.Q., 2012. Chemical insights into Ginseng as a resource for natural antioxidants. Chemical Reviews, 112: 3329-3355.
9. Luo, J.Z. and L. Luo, 2008. Ginseng on Hyperglycemia: Effects and Mechanisms. Evid. Based Complement Alternat. Med., 6(4): 423-7.
10. Vuksan, V., J.L. Sievenpiper, V.Y. Koo, T. Francis, U. Beijan-Zdravkovic and Z. Xu, 2000. American ginseng (*Panax quinquefolius* L.) reduces postprandial glycemia in nondiabetic subjects and subjects with type 2 diabetes mellitus. Arch. Intern. Med., 160: 1009-13.
11. Gum, S.I., S.J. Jo and S.H. Ahn, 2007. The potent protective effect of wild ginseng (Panax ginseng C.A. Meyer) against benzo[á]pyrene-induced toxicity through metabolic regulation of CYP1A1 and GSTs. Journal of Ethnopharmacology, 112(3): 568-576.
12. Wang, R., J. Kong, D. Wang, L. Lien and E.J. Chi Lien, 2007. Survey of Chinese herbal ingredients with liver protection activities. Chinese Medicine, 2:5 doi: 10.1186/1749-8546-2-5.
13. Sena, S., S. Chena, B. Fenga, Y. Wua, E. Luib and S. Chakrabartia, 2011. American ginseng (Panax quinquefolius) prevents glucose-induced oxidative stress and associated endothelial abnormalities. Phytomedicine, 18: 1110- 1117.
14. Ravindran, P.N., B.K. Nirmal and K. Sivaraman, 2007. The Genus Curcuma. Medicinal and Aromatic Plants - Industrial Profiles. Publisher: CRC, 1st Edition.
15. Krishnaswamy, K. 2008. Traditional Indian spices and their health significance. Asia Pac. J. Clin. Nutr., 17(S1): 265-268.
16. Suryanarayana, P., M. Saraswat, T. Mrudula, T.P. Krishna, K. Krishnaswamy and G.B. Reddy, 2005. Curcumin and turmeric delay streptozotocin-induced diabetic cataract in rats. Invest. Ophthalmol. Vis. Sci., 46: 2092-9.
17. Rivera-Espinoza1, Y. and P. Muriel, 2009. Pharmacological actions of curcumin in liver diseases or damage. Review Article, Liver International ISSN pp: 1478-3223.
18. Epstein, J., R. Sanderson and T. MacDonald, 2010. Curcumin as a therapeutic agent: the evidence from *in vitro*, animal and human studies. British Journal of Nutrition, 103: 1545-1557.
19. Shankar, T.N., N.V. Shantha, H.P. Ramesh, I.A. Murthy and V.S. Murthy, 1980. Toxicity studies on turmeric (*Curcuma longa*): acute toxicity studies in rats, guineapigs & monkeys. Indian J. Exp. Biol., 18(1): 73-5.
20. Qureshi, S., A.H. Shah and A.M. Ageel, 1992. Toxicity studies on *Lpinia galanga* and Curcuma longa. Planta Med., 58(2): 124-7.
21. Shoba, G., D. Joy, T. Joseph, M. Majeed, R. Rajendran and P.S. Srinivas, 1998. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. Planta Med., 64(4): 353-6.
22. Lao, C.D., M.F. Demierreand and V.K. Sondak, 2006. Targeting events in melanoma carcinogenesis for the prevention of melanoma. Expert Rev. Anticancer Ther., 6(11): 1559-68.
23. Reeves, P.G., F.H. Nielsen and G.C. Fahmy, 1993. Reported of the American Institute of Nutrition adhoc writing committee on the reformulation of the AIN-76 A Rodent diet. J. Nutr., 123: 1939-1951.
24. A.O.A.C., 1975. Official Methods of Analysis of Assoc. of official agricultural chemists. 12th Ed. Washington, D. C.

25. Jayasekhar, P., P.V. Mohanan and K. Rahinam, 1997. Hepatoprotective activity of ethyl acetate extract of acacia catechu. Indian Journal of Pharmacology, 29: 426-428.
26. Lazarow, A. and B. Palay, 1954. Experimental Diabetes and its Relation to Disease. A Symposium Blackwell Scientific Publication Oxford.
27. Fossati, P., L. Orencipl and G. Berti, 1980. Egyptian Colorimetric Method of Determination of Uric Acid in Serum. Clin. Chem., 26: 227.
28. Patton, C.J. and S.R. Crouch, 1977. Enzymatic colorimetric method to determine urea in serum. Anal. Chem., 49: 464.
29. Bartels, H. and M. Bohmer, 1971. Creatinine standard and measurement of serum creatinine with picric acid. Clin. Chem. Acta, 32: 81.
30. Allain, C.Z., L.S. Poon and C.S. Chan, 1974. Enzymatic determination of total serum cholesterol. Clin. Chem., 20: 470-475.
31. Foster, L.B. and T.T. Dumns, 1973. Determination of triglycerides. J. Clin. Chem.; 19: 338 -353.
32. Lopes-Virella, M.F., S. Stone, S. Ellis and J.A. Collwellm, 1977. Cholesterol determination in high-density lipoproteins separated by three different methods. Clin. Chem., 23(5): 882-893.
33. Fried Wal, W.T., R.I. Leve and D.S. Fredrickson, 1972. Estimation of the concentration of low-density lipoprotein separation by three different methods. Clin. Chem., 18: 499-502.
34. Trinder, P., 1959. Determination of blood glucose using U-Amino penzanone. J. Clin. Path., 22: 246.
35. Reitman, S. and S. Frankel, 1957. Determination of glutamate pyruvate transferase. Am. J. Clin. Path., 28: 56.
36. Kind, P.R.N. and E.J. King, 1954. Estimation of plasma phosphatase by determination of hydrolysed phenol with amino-antipyrine. J. Clin. Path., 7: 322-326.
37. Steel, R.G. and J.H. Torri, 1980. Principal and Procedures of Statistical, Biometrical Approach. Pbl. McGrew Hill Book Company. 2nd Ed. New York, U.S.A.
38. Moscatiello, S., R. Manini, G. Marchesini, J.Z. Luol and L. Luo, 2007. American Ginseng Stimulates Insulin Production and Prevents Apoptosis through Regulation of Uncoupling Protein-2 in Cultured β Cells. Nutrition, Metabolism & Cardiovascular Diseases, 17: 63-70.
39. Schena, F.P. and L. Gesualdo, 2005. Pathogenetic mechanisms of diabetic nephropathy. J. Am. Soc. Nephrol., 16(1): S30-3.
40. Chiu, J., A. Khan Zia, H. Farhangkhoee and S. Chakrabarti, 2009. Curcumin prevents diabetes-associated abnormalities in the kidneys by inhibiting p300 and nuclear factor-B. Nutrition, 25: 964-972.
41. Steffes, M.W., R. Osterby, B. Chavers and S.M. Mauer, 1989. Mesangial expansion as a central mechanism for loss of kidney function in diabetic patients. Diabetes, 38: 1077-1081.
42. Sena, S., S. Chena, B. Fenga, Y. Wua, E. Luib and S. Chakrabartia, 2012. Preventive effects of North American ginseng (*Panax quinquefolium*) on diabetic nephropathy. Phytomedicine, (19): 494-505.
43. Koracevic, D., G. Koracevic, V. Djordjevic, S. Andrejevic and V. Cosic, 2001. Method for the measurement of antioxidant activity in human fluids. J. Clin. Pathol., 54(5): 356-361.
44. Pandya, U., M.K. Saini, G.F. Jin, S. Awasthi, B.F. Godley and Y.C. Awasthi, 2000. Dietary curcumin prevents ocular toxicity of naphthalene in rats. Toxicol. Lett., 115(3): 195-204.
45. Kim, J.S., K.W. Kim, K.J. Choi, Y.K. Kwak, K.H. Lee and H.Y. Chung, 1996. Screening of antioxidative components from red ginseng saponin. Korean J. Ginseng Sci., 20: 173-178.
46. Dixit, V.R., P. Jain, K. Bhandari and A.K. Purohit, 1991. Korean red ginseng attenuates hypercholesterolemia-enhanced platelet aggregation through suppression of diacylglycerol liberation in high-cholesterol-diet-fed rabbits. Phytother. Res., 22(6): 778-783.
47. Hwang, S.Y., D.J. Son, I.W. Kim, D.M. Kim, S.H. Sohn, J.J. Lee and S.K. Kim, 2008. Korean red ginseng attenuates hypercholesterolemia-enhanced platelet aggregation through suppression of diacylglycerol liberation in high-cholesterol-diet-fed rabbits. Phytother. Res., 22(6): 778-783.
48. Jung, C.H., H.M. Seog, C. Iwm, H.D. Choi and H.Y. Cho, 2005. Effects of wild ginseng (Panax ginseng C.A. Meyer) leaves on lipid peroxidation levels and antioxidant enzyme activities in streptozotocin diabetic rats. J. Ethnopharmacol., 98: 245-250.
49. Farhangkhoee, H., Z.A. Khan, S. Chen and S. Chakrabarti, 2006. Differential effects of curcumin on vasoactive factors in the diabetic rat heart. Nutr. Metab., 3: 27-34.
50. Sharma, S., S.K. Kulkarni and K. Chopra, 2006. Curcumin, the active principle of turmeric (*Curcuma longa*), ameliorates diabetic nephropathy in rats. Clin. Exp. Pharmacol. Physiol., 33: 940-5.

51. Suryanarayana, P., A. Satyanarayana, N. Balakrishna, P.U. Kumar and G.B. Reddy, 2007. Effect of turmeric and curcumin on oxidative stress and antioxidant enzymes in streptozotocin-induced diabetic rat. Med. Sci. Monit., 13(12): 286-92.
52. Luo, J.Z. and L. Luo, 2006. American Ginseng Stimulates Insulin Production and Prevents Apoptosis through Regulation of Uncoupling Protein-2 in Cultured β Cells. Evid. Based Complement Alternat, Med., 3(3): 365-72.
53. Sesti, G., 2002. Apoptosis in the beta cells: cause or consequence of insulin secretion defect in diabetes?. Ann. Med., 34: 444-50.
54. Lee, W.K., S.T. Kao, M.I. Liu and J.T. Cheng, 2006. Increase of insulin secretion by ginsenoside Rh2 to lower plasma glucose in wistar rats. Clin. Exp. Pharmacol. Physiol., 33: 27-32.
55. Rudorf, D.C., 2000. Ginseng Continuing Education Module. New Hope Institute of Retailing Certificate of Completion in Natural Healing.
56. Deshpande, U.R., S.G. Gadre and A.S. Raste, 1998. Protective effect of turmeric (*Curcuma longa* L.) extract on carbon tetrachloride-induced liver damage in rats. Indian J. Exp. Biol., 36(6): 573-7.
57. Kim, H.G., S.R. Yoo and H.J. Park, 2011. Antioxidant effects of Panax ginseng C.A. Meyer in healthy subjects: a randomized, placebo-controlled clinical trial. Food and Chemical Toxicology, 49(9): 2229-2235.
58. Ramesh, T., S.W. Kim and J.H. Sung, 2012. Effect of fermented Panax ginseng extract (GINST) on oxidative stress and antioxidant activities in major organs of aged rats. Experimental Gerontology, 47(1): 77-84.
59. Shim, J.Y., M.H. Kim, H.D. Kim, J.Y. Ahn, Y.S. Yun and J.Y. Song, 2010. Protective action of the immunomodulator ginsan against carbon tetrachloride-induced liver injury via control of oxidative stress and the inflammatory response. Toxicology and Applied Pharmacology, 242(3): 318-325.
60. Shukla, R. and M. Kumar, 2009. Role of Panax ginseng as an antioxidant after cadmium-induced hepatic injuries. Food and Chemical Toxicology, 47(4): 769-773.
61. Yokozawa, T., K.S. Kang, N. Yamabe and H.Y. Kim, 2007. Therapeutic potential of heat-processed Panax ginseng with respect to oxidative tissue damage. Drug Discovery & Therapeutics, 1(1): 30-44.
62. Lee, H.J., J.H. Kim, S.Y. Lee, J.H. Park and G.S. Hwang, 2012. Processed ginseng protects t-BHP-induced oxidative damage in HepG2 cells. In Proceedings of the Spring International Ginseng Conference, p. 99. The Korean Society of Ginseng, Jeju, Korea, April 2012.
63. Kwon, Y.S., K.H. Jang and I.H. Jang, 2003. The effects of Korean red ginseng (Ginseng Radix Rubra) on liver regeneration after partial hepatectomy in dogs. Journal of Veterinary Science (Suwon-si, Korea), 4(1): 83-92.
64. Bak, M.J., M. Jun and W.S. Jeong, 2012. Antioxidant and hepatoprotective of the red ginseng essential oil in H2O2-treated HepG2 cells and CCl4-treated mice. International Journal of Molecular Sciences, 13(2): 2314-2330.
65. Kang, K.S., N. Yamabe, H.Y. Kim and T. Yokozawa, 2007. Effect of sun ginseng methanol extract on lipopolysaccharide-induced liver injury in rats. Phytomedicine, 14(12): 840- 845.