Hypolipidemic and Hypocholesterolemic Effects of *Artemisia* and *Lepidiumsativum,* Alcoholic Extracts in Male Rats

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Abstract: The study aimed to examine the impact of oral gavage of *Artemisia* and *Lepidiumsativum* alcoholic extracts on serum levels of insulin, glucose, leptin, lipids profile and antioxidant enzymes in diabetic rats. Sixty male adult rats divided into six equal groups. Group (1) negative control (NC), while the other five groups were fed on high fat and high cholesterol diet for four weeks to induce hypercholesterolemia, then injected with alloxan (150 mg/Kg b. wt) as a single dose, subcutaneously to induce experimental diabetes. Group (2) positive control (PC), while groups (3- 6) were orally administered *Artemisia* extract and *Lepidiumsativum* extract in doses of hundred and two hundred mg/kg., respectively, once daily during experimental period. After 28 days all rats were sacrificed. Antioxidant enzymes were determined in liver homogenate tissues while the other tested parameters were determined in blood serum. The results illustrated that the high dose of *Artemisia* and *Lepidiumsativum* extracts significantly decreased serum insulin hormone, glucose, leptin, TC, TG, LDL and VLDL compared to CP. While the high dose of both extracts increased antioxidant enzymes activity and HDL-c. Conclusively, alcoholic extracts of *Artemisia* and *Lepidiumsativum* at the high dose had the best effects. This study recommended that alcoholic extracts of *Artemisia* and *Lepidiumsativum* are useful for patients who suffer from hypercholesterolemia and diabetes.

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1. Introduction

Hyperlipidemia is defined as a an increasing in blood lipids which considerably the main factors for heart disease [1]. American Heart Association (1994) demonstrated that hypercholesterolemia is an accumulation of LDL plasma lipoprotein [2]. Caused by disease or medication[3].

The most prevalent metabolic diseases worldwide are diabetes characterized by reducing secretion of insulin, insulin action, or both[4]. Diabetes has many Complications such as heart disease, renal failure and blood vessels [5]. All of these diseases regarded to hyperglycemia which in turn result in oxidative stress [6]. The medicinal plants play an important role as antidiabetic medicine it had been used nowadays in the diabetes treatments[7].

Artemisia, is about 1500 species, has been a wealthy supply of natural medicine in many nations [8-9]. *Artemisia* used as antidiabetic medicine[10]. It had been mentioned to lessen oxidative stress related to hyperlipidemia [11].

Lepidium Sativum L., is an annual herb, the seeds are wildly used in the treatment of hyperglycemia and hyperlipidemia [12-13]. Shinde *et al*.[12] reported that *Lepidiumsativum* L. seeds have antioxidant activity which in turn reduce coronary heart disease associated with obesity. Therefore, the reason of this study was to identify the impact of oral gavage of *Lepidiumsativum* and *Artemisia* alcoholic extracts on hypercholesterolemic diabetic male rats.

2. Material and Methods

Chemicals and Drugs

All chemicals with high analytical grade and alloxan will be purchased from Sigma, USA. The tested kits for determinations of glucose, insulin, liptin, total cholesterol, triglycerides, lipoprotein fractions, as well as antioxidant enzymes was purchased from Biosystems (Barcelona, Spain).

Plant

Dried *Artemisia* leaves and *Lepidiumsativum* seeds were obtained from iHerb.com, HERB PHARM, Saudi Arabia.

Experimental animals

A total of 60 adult Male Wister albino rats, weighing 160 ± 5 grams, will be purchased from King Fahd Medical Research Center. Basal diet constituents will be purchased from Baghafar Company for Pharmaceutical and Chemical, Jeddah, KSA.

Basal diet preparation, cholesterol and diabetes induction

Diet was set as described in Reeves et al. [14]. Hypercholesterolemia was induced by nourishing rats with diet rich in cholesterol (2%) and bile salt (0.5%) for 4 weeks by using the technique defined by Shinnick *et al*. [15] Then, Diabetes was induced by injection with alloxan subcutaneously in a dose of 150 mg/kg b.wt. as a single dose [16].

Preparation of plant extract

The methanol extract become organized via soaking 200 g of dry *Artemisia* leaves and *Lepidiumsativum* seeds in one liter of ninety% ethyl alcohol with day by day shaking for 5 days and stored in a refrigerator. The ethanol evaporated by using rotatory evaporator apparatus (synthetic in Russia) attached with a vacuum pump. Twenty grams of both extract (semisolid) have been suspended in a hundred ml distilled water with 2 ml of Tween 80 (postponing agent) to prepare a twenty% alcoholic extract.

Experiment and grouping of rats

The 60 male Wister rats weighing about 160±5 g was used in the study. The animals were housed in cages and was fed on standard chow and water *ad libitum* in a steady environment (room temperature 22 ± three °C, room humidity 50 ± five%) with a 14 h mild and 10 h darkish cycle. The animals were kept beneath observation for one week previous to the beginning of the experiment. After acclimatization period, rats were divided into two main groups. Group (I) (n=10) (NC) fed on normal diet. Group (II) (n=50) was fed on high fat high cholesterol diet for four weeks to induce hypercholesterolemia, after that all 5 groups fasted for 12 hrs before injected with alloxan to induce diabetes. Rats were given glucose solution (10%) in feeding bottles for 24 hrs to prevent hypoglycemia. Then, after 3 days, fasting blood samples were collected from tail vein of all surviving rats to analyze glucose level Shah, and Khan [17]. Diabetic rats were distributed into 5 sub- groups (n=10 rats each group) and all rats were fed on rat pallets. The groups will be kept as follows:

Group (1): Control negative group (NC)

Group (2): Control positive group (PC)

Group (3): Treated with *Artemisia* (100 mg/kg) (LD)

Group (4): Treated with *Artemisia* (200 mg/kg) (HD)

Group (5): Treated with *Lepidiumsativum* (100 mg/kg) (LD)

Group (6): Treated with *Lepidiumsativum* (200 mg/kg) (HD)

At day twenty eight blood samples were collected for biochemical analyses. liver was taken for antioxidant enzymes determination.

Determination of biological evaluation

Each day feed intake (FI) for all groups were recorded throw out the experimental time (8 weeks). Body weight gain percentage (BWG %) and feed efficiency ratio (FER) were calculated consistent with the approach of [18].

Determination of serum blood lipid

Total cholesterol, triglycerides, lipoprotein fractions level were assessed by commercial chemical kits protocol [19].

Determination of hepatic antioxidant enzymes activity

Antioxidant activities of hepatic enzymes (glutathione peroxidase, superoxidase dismutase, and catalase) were measured according to Paglia and Valentaine [20].

Statistical analysis

All results were presented as the mean ± SD. Data were evaluated using SPSS 22 for windows. An analysis of variance, L.S.D. test will be performed to test the differences in the treatment [21].

3. Results and Discussion

Feed intake was increased in the PC as compared to NC rats. Administration either *Artemisia* or *Lepidiumsativum* alcoholic extracts led to significant decrease in FI. The BWG% significantly decreased in PC compared with NC rats. Treatment with *Artemisia* and *Lepidiumsativum* alcoholic extracts improved the BWG% compared to PC group Table (1). These results agreed with those found by Sjoslrom *et al*. [21] Sharma *et al.* [22] and Boriky *et al.* [23] who found that the FI and BWG% of PC was markedly reduced. Administration of *Artemisiaabsinthium* for 6 weeks increased considerably the feed intake and the body weight. Kamal and Jamil [24] found that decreased body weight in diabetic rats due to DM, while after treatment of A*rtemisia sieberi*, their weight increased again. This could be attributed to improved glycemic level by *Artemisia sieberi* extract. The same effect was found in *Lepidiumsativum* as reported by Eddouks and Maghrani [25].

Administration of *Artemisia* and *Lepidiumsativum* alcoholic extracts to hypercholesterolemic diabetic rats for 4 weeks showed reduction in glucose, insulin hormone and leptin levels (p<0.05) compared with NC rats as shown in Table (2). These results agreed with Al-Waili [26] who showed that *Artemisia herbaalba* extract (AHE) contains active compounds that have the capacity to reduce hyperglycemia. Norio Yamamoto *et al*. [27] suggested that regulating the secretion of leptin by ethanol extract of *Artemisia princeps* (APE) may inhibit fatty acid synthase and accumulation of triglyceride in the liver, thus improve glucose tolerance. The obtained results were similar to Kamal and Jamil [24], Marrif *et al*. [28] and Twaij and Al-Badr [29]. Moreover, *Artemisia sieberi* hypoglycemic effect may explained by increased peripheral glucose utilization. *Lepidiumsativum* extract caused a potent inhibition of renal proximal tubular glucose reabsorption which contribute in lowering hyperglycemic effect. This renal effect is at least one mechanism explaining the observed hypoglycaemic activity of this plant in normal and diabetic rats [25].

Table (1): Effect of alcoholic extracts of *Artemisia* and *Lepidiumsativum* on biological evaluation in hypercholesterolemic diabetic rats

Experimental groups	FI (g/day)	BWG%
NC	17.8	5.66 ±.21 [a]
PC	33.5	1.71 ±0.84 [c]
Artemisia LD	28.7	2.89 ± 0.08 [b]
Artemisia HD	24.5	4.38 ± 0.11 [a]
Lepidiumsativum LD	28.4	3.10 ± 1.09 [b]
Lepidiumsativum HD	26.1	3.43± 0.52 [a]

Means (n=10 rat) with different letters in the same column considered significant (P < 0.05)

Table (2): Effect of alcoholic extracts of *Artemisia* and *Lepidiumsativum* on serum levels of insulin hormone, glucose and leptin in hypercholesterolemic diabetic rats

Experimental groups	Insulin hormone (µU/ml)	Glucose (mg/dl)	Leptin (ng/ml)
NC	8.54 ± 0.36[a]	95.11 ± 2.12 [a]	29.0 ± 1.6 [c]
PC	5.11 ±.46 [d]	186.23 ± 1.96 [d]	43.7 ± 2.3 [a]
Artemisia LD	5.74 ± 1.19 [d]	181.07± 1.13 [d]	40.3 ± 0.9 [a]
Artemisia HD	7.59 ± 1.82 [c]	127.33 ± 1.74 [b]	32.4 ± 1.4 [c]
Lepidiumsativum LD	5.77± 3.128 [d]	180.62 ± 2.62 [d]	40.6 ± 1.3 [a]
Lepidiumsativum HD	7.61 ± 2.33[c]	127.24±2.93 [b]	32.8± 0.98 [c]

Means (n=10 rat) with different letters in the same column considered significant (P < 0.05)

Table (3): Effect of alcoholic extracts of *Artemisia* and *Lepidiumsativum* on serum total cholesterol (TC) and triglycerides (TG) levels in hypercholesterolemic diabetic rats

Experimental groups	TC (mg/dL)	TG (mg/dL)
NC	91.645 ± 2.14 [e]	41.81 ± 2.34 [d]
PC	169.645 ± 3.33 [a]	98.23 ± 1.53 [a]
Artemisia LD	149. ± 2.61 [b]	81.62± 1.16 [b]
Artemisia HD	104.54 ± 0.88 [de]	45.31 ±1.45 [d]
Lepidiumsativum LD	146.± 1.84 [b]	78.94± 2.28 [b]
Lepidiumsativum HD	100.62 ±3.14[de]	43.61 ±2.12 [d]

Means (n=10 rat) with different letters in the same column considered significant (P < 0.05)

Treatment with high dose of *Artemisia* and *Lepidiumsativum* alcoholic extracts to hypercholesteromic diabetic rats significantly diminished TC and TG levels compared to the PC group Table (3). These finding agreed with Zhong [30] who found that *Artemisiacapilaris* extract reduced TC concentration in hyperlipidemic mice by improving metabolism. Weng and Chen [31] demonstrated that *Artemisia scoparia* reduced atherosclerotic lesion in hypercholesterolemic rabbits by decreasing TC and TG concentrations. In addition, Dinani *et al*. [32] indicated that *Artemisia aucheri* significantly improved lipid parameters in hypercholesterolemic rats, thus could be used as herbal remedies for atherosclerosis. Aqueous extract of *Artemisia sieberi* has antidiabetic and hypolipideamic effects in alloxan-induced diabetic rats. Moreover, hypolipideamic effect of *Lepidiumsativum* could be explained by its antioxidant activity through the presence of many active compounds asphenolic and flavonoids [33].

From data recorded in Table (4) large doses of *Artemisia* and *Lepidiumsativum* alcoholic extracts when given by gavage to hypercholesterolemic diabetic rats diminished significantly LDL-c and VLDL-c levels with increased HDL-c compared to PC group. Kamal *et al*. [34] reported that administration of *Artemisia sieberi* exhibited noticeable hypolipidemia effect in diabetic rats, thus could be attributed to its antioxidant compounds. *Artemisia absinthium* treatment alleviated lipid profiles in diabetic rats [35- 36]. Moreover, *Lepidiumsativum* significantly improved lipid parameters in hypercholesterolemic rats thus could be explained by its antioxidant activity [33, 37].

Significant decrease in hepatic antioxidant enzymes activity was found in PC compared to NC rats data shown in Figures (1-3). Dallak and Bin-Jaliah [38] reported that injection of alloxan-induced diabetes, which exhibited diminished in antioxidant enzymes SOD and CAT along with elevated lipid

peroxidation. Thus could be used as an indicator for generated free radicals. Oral administration of *Artemisia* and *Lepidiumsativum* alcoholic extracts showed significant increased compared to PC rats Figures (1-3). These data agree with Han *et al*. [39], Kim *et al* [40] and Juteau *et al*. [41]. Shinde *et al*. [42] demonstrated that the activities of SOD, CAT and level of GSH-Px were elevated and level of MDA declined significantly in the *Lepidiumsativum* in nephrotoxic rats. This is due to its antioxidant activity [43].

Table (4): Effect of alcoholic extracts of *Artemisia* and *Lepidiumsativum* on serum levels of lipoprotein fractions in hypercholesterolemic diabetic rats

Experimental groups	HDL (mg/dL)	LDL (mg/dL)	VLDL (mg/dL)
NC	45.55 ± 3.22 ^{c}	37.733 ± 1.83 ^{e}	8.362± 1.92 ^{d}
PC	32.46 ± 1.86 ^{a}	117.539 ±.37 ^{a}	19.646± 2.18 ^{a}
Artemisia LD	33.94 ± 4.61 ^{a}	98.736 ± 1.82^{ab}	16.324± 1.73^{b}
Artemisia HD	41.65 ± 2.62 ^{bc}	53.828 ± 1.87 ^{d}	9.062 ± 2.31 ^{d}
Lepidiumsativum LD	32.78 ± 3.19 ^{a}	96.432 ±.97 ^{ab}	15.788 ±.26 ^{b}
Lepidiumsativum HD	42.43± 0.77 ^{bc}	49.468 ±2.73 ^{d}	8.722 ±.79 ^{d}

Means (n=10 rat) with different letters in the same column considered significant (P < 0.05)

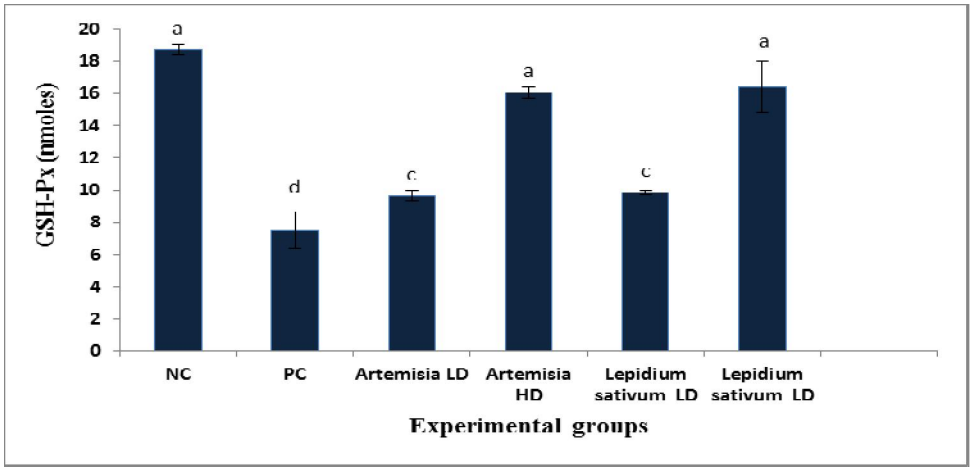

Figure (1): Effect of alcoholic extracts of *Artemisia* and *Lepidiumsativum* on hepatic glutathione peroxidase (GSH-Px) activity

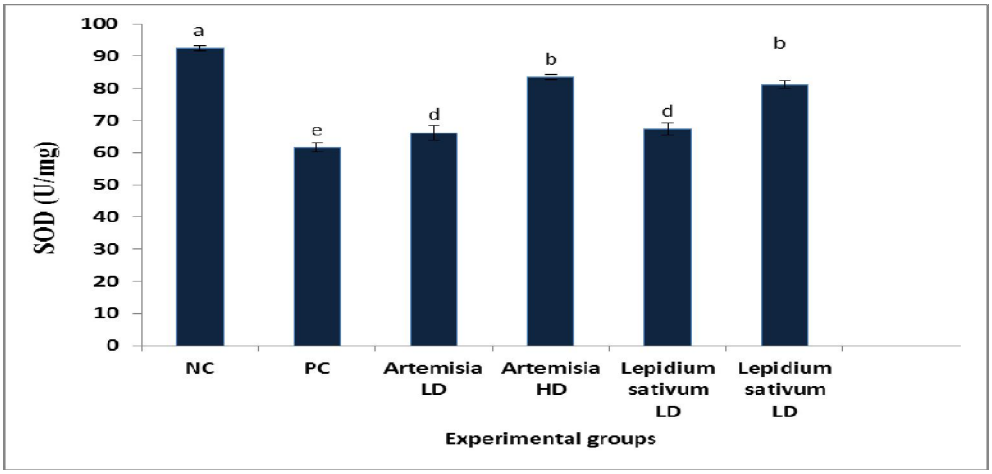

Figure (2): Effect of alcoholic extracts of *Artemisia* and *Lepidiumsativum* on hepatic superoxide dismutase (SOD) activity

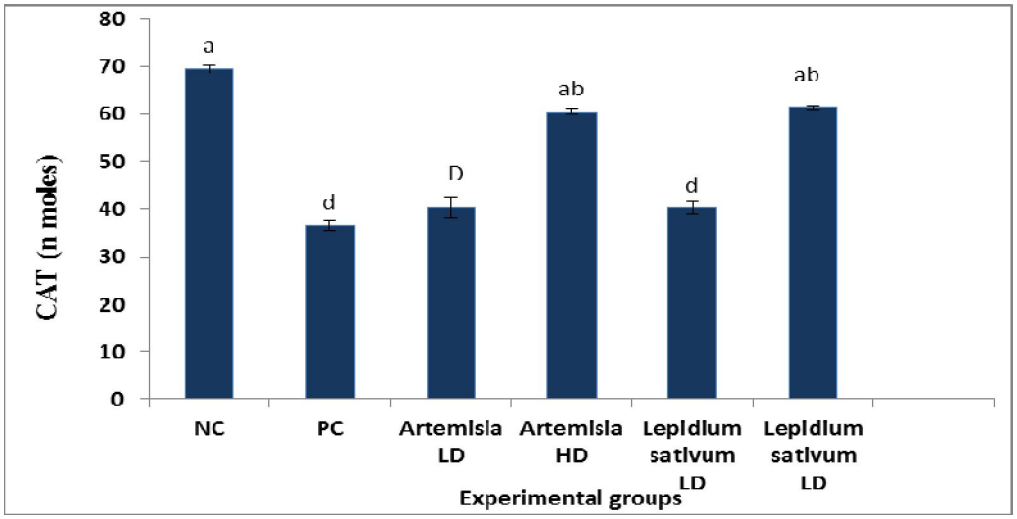

Figure (3): Effect of alcoholic extracts of *Artemisia* and *Lepidiumsativum* on hepatic catalase (CAT) activity

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