

Glucose and Lipid-Lowering Activities of Some Bioactive Extracted Components from Herbs (Camellia Sinensis, Matricaria Chamomilla and Carum Carvi) in Streptozotocin-diabetic Rats: Intelligent Method for Herbal Medicines Production with Selected Active Ingredients

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Abstract

Diabetes mellitus (DM, Type 2 diabetes) is a metabolic syndrome categorized by irregular discharge of insulin that subsequently disturbs glucose breakdown. It is the most prevalent chronic non-communicable increasing disease globally and has a great impact on human health. Many treatments have been recently proposed for this disease like insulin and medicine therapies. However, some of these treatments have shown slight efficacy practically with many side effects, thus, searching for new classes of natural and safe compounds has a global demand.

Based on the many reported pharmacological effectivity of *Camellia Sinensis*, *Matricaria Chamomilla*, and *Carum Carvi*, evaluation of the glucose and lipid-lowering properties of some extracts of such plants by some polar and nonpolar organic and aqueous solvents in streptozotocin-diabetic mice and rats were done in the research.

The results showed that some extracts of *Camellia Sinensis*, *Matricaria Chamomilla*, and *Carum Carvi* can properly lower serum glucose and reverse inappropriate changes regarding serum lipids including triglyceride, cholesterol, HDL-cholesterol, as well as LDL-cholesterol in diabetic experimental animals. To conclude, all of these herbal remedies with multiple bioactive components are of potential benefit in the management of diabetes mellitus.

Introduction

Diabetes mellitus is a chronic non-communicable malady which occurs when the pancreas cannot produce insulin, or when the body cannot use insulin properly. In addition, it resulted from many impairments like fat, carbohydrate and protein metabolism by either wrong amount of insulin production or decreased sensitivity of target tissue to insulin (1, 2).

Type 1 Diabetes Mellitus (T1DM) includes impaired β -cells of the pancreas and decreasing or no insulin production whereas Type 2 Diabetes mellitus (T2DM) is determined by the resistance of target tissue to insulin and the relative rarity of insulin made by the islet β -cells (3, 4).

The escalation in the prevalence of diabetes could be attributed to mainly genetic susceptibility and lifestyle modifications. Additionally, the failure to properly control hyperglycemia and adverse effects associated with the current conventional drugs (5) could be another reason. These limitations motivated researchers to search for alternative therapies for diabetes which natural products, particularly plants are of interest. The choice of plants is because they are made in a biological system, and could interact better than chemical drugs with protein targets and are more likely to succeed as drugs. Studies have reported that ethnopharmacology is a major tool in the search for herbal remedies from medicinal plants (6).

Former studies showed the importance given by diabetics to traditional plant medicine and these medicinal plants play a key role in the treatment of diabetes mellitus. Herbal medicines have been traditionally used due to several advantages; they are effective, economical, and accessibility, and there is no resistance evidence to plants' extracts (7).

Besides hyperglycemia, many other factors like dyslipidemia or hyperlipidemia are too engaged in the development of complexity in diabetic patients that are known as the main causes of morbidity as well as mortality(8).

Camellia sinensis (L.) Kuntze (green tea, I), the major variety is *C. sinensis* var. *assamica* (J.W. Mast.) Kitam, a plant native to China and Southeast Asia, is globally a very important plant for humans. The *Camellia sinensis* plant obtains a wide diversity of black, green, oolong, yellow, brick dark, as well as white tea. According to fermentation degree, teas are categorized into dark tea (post-fermented tea), black tea (fermented tea), oolong, yellow and white tea (partly fermented), as well as green tea (completely fermented). However, green tea has been preferred more as compared with other teas for its many health care benefits. Because of its greater antioxidant content, green tea is being used as a nutritional supplement or even nutraceutical aid. Previous studies showed its beneficial biological properties for a wide heterogeneity of disorders, like antidiabetes, antiobesity, anti-inflammatory, anticancer, neuroprotective, antibacterial, antiviral, antifungal, as well as antiglaucoma activities (4, 9–13).

Chamomile (*Matricaria chamomilla* L., *Matricaria recutita*, German chamomile, II) is a famous medicinal herb that belongs to the daisy family (Asteraceae/Compositae). In recent years, chamomile has been used as an anti-diabetic, anti-pain, anti-oxidant, anti-cancer, as well as anti-inflammatory agent for possesses various classes of bioactive ingredients like flavonoids and terpenoids(14, 15). Some former studies have shown that chamomile contributes to the hindrance of oxidative stress in patients with type 2 diabetes mellitus,

differentiation of mesenchymal stem cells (MSCs) into insulin-making cells, and potential activity for glucose lowering in streptozotocin (STZ)-induced diabetic rabbits(16–23).

Caraway (*Carum carvi* L., III) belonging to the Apiaceae family seen in western Asia, Europe, as well as North Africa and its phytotherapy knowledge has been much developed (24, 25). This plant has been used since ancient times, especially in digestive disorders treatment. Caraway is known globally as antibacterial, antiulcerogenic, and antiproliferative and is used for treating diabetes, cardiovascular and hypertension diseases, and plasma lipid parameters(26).

In this paper, because on our relevant former studies (27–30) and because of the mentioned remarkable blood glucose and lipid-lowering properties of these herbal medicines, different polarity' extracts of I-III with organic and aqueous solvents were studied for these pharmacological activities and the outcomes were compared to the control as well as STZ-diabetic mice and rats.

Materials and methods

General

Ethanol, Carbon tetrachloride, Chloroform, Streptozotocine (STZ) as well as other chemicals were obtained from Merck (Darmstadt-Germany) and Sigma-Aldrich chemical Companies (the US).

Gas chromatography analysis

Gas chromatographic analysis was done on an Agilent 7890N chromatograph paired with a MS 5975C, MODE EI. A capillary column, HP-5MS (30 m x 0.25 mm i.d.; the film thickness 0.25 μ m) was applied. The column operating conditions were as follows: 60°C for 2 min and then 7°C/min. to 280°C. The carrier gas, helium at the rate of 1 ml/min. Samples (1 μ l) of diluted essential oils were manually injected.

Components identification

The parts of extracts were identified through their retention time and retention indices which are related to C₆-C₃₅ n-alkanes computer matching with Wiley/NIST library and comparing their mass spectra with the genuine samples with available data in the literature. The proportion of composition of the compounds was evaluated from the GC peak area with no correction factor that calculated relatively.

Plant material, Preparing hydroethanolic, chloroform, carbon tetrachloride as well as aqueous extracts

Leaves of *Camellia Sinensis*, seeds of *Carum Carvi*, and the aerial parts of *Matricaria Chamomilla* were provided from the local market in Tehran and authenticated in the herbarium of the university (Voucher Numbers: 511-PMP/A, 1621-AUPF and 51L-PMP/A, respectively). Plants were protected from the sunlight. Then air-dried in the shade, powdered carefully, then extracted by maceration with the mentioned solvents with different polarities (70% ethanol-water, chloroform, carbon tetrachloride, as well as aqueous) separately for 72 hours (100 g of the powdered plant mashed in 500 ml solvent). Then the mixtures were filtered and concentrated to yield the extracts which were used for GC-MS analysis, antidiabetic also antilipidemic activities on experimental animals.

Pharmacological methods

Animals

30 NMRI mice weighing 30 to 35 g and 88 adult male Wistar rats weighing 180 to 250 g (Pasteur's Institute in Tehran-Iran) were placed in an air-conditioned animal house room at 22 $\pm$ 2°C and provided with standard diet as well as tap water. The procedures were in accordance with NIH guidelines for the care and use of research animals.

Experimental protocol

Rats and mice were desultorily divided into control, diabetic, diabetic + chloroform, diabetic + carbon tetrachloride, diabetic + hydroalcoholic as well as diabetic + aqueous extract groups (200 mg/kg). Experimental animals were made diabetic by an injection of streptozotocin (STZ; 60 mg/kg, *i.p.*) dissolved in cold physiologic saline. Diabetes was verified by the presence of hyperglycemia, polyphagia, polydipsia, and polyuria as well as weight loss a week later. Three weeks after the STZ injection, blood samples were picked and serum glucose concentrations were measured by applying the glucose oxidation method (Parsazmun-Tehran). Merely the animals with serum glucose over 250 mg/dl were picked for more experiments. The extracts were daily and *i.p.* administered relevant groups starting from 0 to three weeks after STZ injection. Alterations of body weight were measured weekly throughout the study. In addition, serum triglyceride, total cholesterol and HDL cholesterol levels were measured by using a spectrophotometer and special kits obtained from Parsazmun (Tehran). LDL-cholesterol level was measured by the Friedwald formula as follows:

$$\text{LDL-cholesterol} = \text{Total cholesterol} - \text{HDL cholesterol} - (\text{triglyceride}/5)$$

Data and statistical analysis

Whole data was illustrated as means $\pm$ SEM. Statistical analysis was conducted by applying repeated measures and one-way analysis of variance (ANOVA), followed by a coupled Tukey *post-hoc statistical* test. A statistical *p-value* under 0.05 was regarded significant.

Results

Chemistry

The desired titled extracts were made from softening of these herbal remedies in the mentioned organic and aqueous solvents. GC-MS results each extract were summarized in Table 1.

Table 1

Quantitative analysis of phytochemicals in hydroethanolic, chloroform, carbon tetrachloride, and aqueous extraction of *Camellia Sinensis* (I), *Matricaria Chamomilla* (II), and *Carum Carvi* (III) identified by GC-MS with many pharmacological activities. (27–30).

No.	Chemical Family	Hydroethanolic (%)			Chloroform (%)			Carbon tetrachloride (%)			Aqueous (%)		
		I	II	III	I	II	III	I	II	III	I	II	III
1	Phenol & Polyphenol	-----	-----	-----	-----	-----	-----	3.2	-----	-----	16.34	-----	-----
2	Fatty acids	60.82	31.02	-----	0.53	-----	63.1	22.38	6.08	16.87	-----	-----	39.48
3	Alcohols	-----	-----	-----	0.17	11.5	-----	-----	3.04	-----	2.23	0.81	-----
4	Caffeine	-----	-----	-----	-----	-----	-----	-----	-----	-----	6.26	-----	-----
5	Carboxylic acids	-----	-----	-----	20.97	35.8	-----	-----	-----	-----	-----	-----	-----
6	Amids	17.52	-----	-----	1	-----	-----	3.05	-----	-----	5.49	-----	-----
7	Terpenes & Sterols	-----	10.89	25.55	-----	-----	18.15	-----	-----	43.81	-----	28.88	8.93
8	Histamines	-----	-----	-----	-----	6.16	-----	-----	-----	-----	-----	-----	-----
9	Hydrazines	-----	-----	-----	-----	2.91	-----	-----	-----	-----	-----	-----	-----
10	Fluoxetine	-----	-----	-----	-----	2.15	-----	-----	-----	-----	-----	-----	-----
11	Guanosine	-----	-----	-----	-----	1.3	-----	-----	-----	-----	-----	-----	-----
12	Amphetamines	-----	-----	-----	-----	2.22	-----	-----	4.88	-----	-----	-----	-----
13	Coumarine	-----	-----	-----	-----	25.81	-----	-----	-----	-----	-----	-----	-----
14	Fenamin	-----	-----	-----	-----	-----	-----	-----	1.19	-----	-----	-----	-----
15	Calciferol (Vitamine D ₃)	-----	-----	-----	-----	-----	-----	-----	1.19	-----	-----	0.72	-----
16	Epinephrine	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0.49	-----
17	Amines	-----	-----	-----	-----	2.11	-----	-----	-----	-----	-----	0.74	-----
18	Others	21.66	58.09	74.45	77.33	10.04	18.75	71.37	83.62	39.32	69.68	68.36	51.19

GC-MS analyses

It showed that in *Camellia Sinensis* (I) extracts, fatty acids, Phenol & Polyphenol were more than the others but in *Carum Carvi* (III) extracts, fatty acids, Terpenes and Sterols were more in the other parts. Also, in *Matricaria Chamomilla* (II) extracts, in addition to fatty acids, Terpenes, and Sterols, other pharmacological components such as Histamines, Amphetamines, and Fluoxetine were extracted by solvents.

Pharmacology

General Consideration

Mortality (death rate), morbidity (known as abnormal conditions or behavior thanks to a disorder), irritability (a condition of aggressiveness or raised response on handling), and other relevant abnormal states were seen in the experimental animals. The motor coordination index (measured by the Rota-rod apparatus, Harvard, UK) didn't show noticeable differences among the treated animals though.

Blood serum glucose, triglyceride (TG), cholesterol, HDL, and LDL in hydroethanolic, chloroform, carbon tetrachloride, and aqueous extracts of *Camellia Sinensis* (I), *Matricaria Chamomilla* (II) and *Carum Carvi* (III)

Body weight, serum glucose, and lipid levels for the groups receiving I-III extracts indicated no significant differences among the groups at baseline (week 0). Three weeks after STZ injection, the control group had a remarkable raise in body weight ($p < 0.05$), and in the diabetic group, a non-significant loss of weight was noticed for all of the extracts related to baseline (week 0), especially in I. Also, no change in body weight in all extracts (I-III) was achieved relative to the diabetic group.

Serum glucose

In the diabetic group, a noticeable rise of serum glucose ($p < 0.001$), and in diabetic groups receiving extracts of I, a little remarkable increase ($p < 0.01$) regarding baseline (week 0) was noticed. The diabetic groups receiving carbon tetrachloride ($p < 0.05$) or ethanolic ($p < 0.01$) extracts of I had a significant reduction of serum glucose versus the diabetic group. In addition, diabetic groups receiving ethanolic ($p < 0.01$), carbon tetrachloride ($p < 0.05$), or essential oil ($p < 0.001$) extracts of II had a significant reduction of serum glucose as compared with the diabetic group. Furthermore, diabetic groups treated with chloroform ($p < 0.05$), essential oil ($p < 0.05$), carbon tetrachloride ($p < 0.01$), or ethanolic ($p < 0.01$) extracts of III had significant reduction of serum glucose as compared with the diabetic group.

Serum triglyceride

There was a significant increase in serum triglyceride in the diabetic group in the third week as compared with the control group ($p < 0.01$). The diabetic groups receiving carbon tetrachloride ($p < 0.05$), ethanolic ($p < 0.01$), or chloroform ($p < 0.05$) extracts of I had a significant reduction of serum triglyceride versus the diabetic group. Also, diabetic groups receiving different extracts of II had no remarkable reduction of serum triglyceride as compared with the diabetic group. Furthermore, diabetic groups treated with chloroform ($p < 0.05$), carbon tetrachloride ($p < 0.01$), or ethanolic ($p < 0.01$) extracts of III had a remarkable reduction of serum triglyceride as compared with the diabetic group.

Total cholesterol

There was a significant increase in serum total cholesterol in the diabetic group in the third week as compared with the control group ($p < 0.01$). The diabetic group receiving ethanolic ($p < 0.05$) extract of I had a significant reduction of serum total cholesterol versus the diabetic group. In addition, diabetic groups receiving essential oil ($p < 0.01$), carbon tetrachloride ($p < 0.01$), or ethanolic ($p < 0.001$) extracts of II had a remarkable reduction of serum total cholesterol as compared to the diabetic group. Furthermore, diabetic groups treated with various extracts of III had no significant reduction of serum total cholesterol as compared with the diabetic group.

Serum HDL

There was a significant decrease in serum HDL in the diabetic group in the third week as compared with the control group ($p < 0.05$). The diabetic group receiving ethanolic ($p < 0.05$) extract of I had a significant increase in serum HDL versus the diabetic group. In addition, diabetic groups receiving different extracts of II had no significant increase in serum HDL as compared with the diabetic group. Furthermore, the diabetic group treated with ethanolic extract ($p < 0.05$) of III had a remarkable increase in serum HDL as compared with the diabetic group.

Serum LDL

There was a significant increase in serum LDL in the diabetic group in the third week as compared with the control group ($p < 0.001$). The diabetic groups receiving carbon tetrachloride ($p < 0.01$), ethanolic ($p < 0.01$), or chloroform ($p < 0.05$) extracts of I had a remarkable reduction of serum LDL versus the diabetic group. In addition, diabetic groups receiving carbon tetrachloride ($p < 0.05$), ethanolic ($p < 0.01$), or essential oil ($p < 0.05$) extracts of II had a significant reduction of serum LDL as compared to the diabetic group. Furthermore, diabetic groups treated with chloroform ($p < 0.05$), essential oil ($p < 0.05$), carbon tetrachloride ($p < 0.01$), or ethanolic ($p < 0.01$) extracts of III had remarkable reduction of serum LDL as compared to the diabetic group.

Discussion

In the recent years, researchers have initiated various new therapeutic agents and methods to treat diabetes as well as other diseases. Herbal medicines and natural products are believed being safe, effective, affordable, and applied to prevent or treat various diseases (16).

These natural medicines also provide therapeutic and supportive effects for DM by various modifications in the body like β -cells regeneration in the pancreas, control of gluconeogenesis as well as loss of glycogen (31, 32), etc.

Bioactive components of such plants having numerous pharmacological properties show a key role in α -amylase and α -glucosidase inhibition. Therefore, they have the management potential towards T2DM (33).

According to numerous pharmacological activities of mentioned herbs (I-III) like glucose- and lipid-lowering effects, hypoglycemic as well as hypolipidemic properties of hydroethanolic, chloroformic, carbon tetrachloride and aqueous extracts of such plants were noticed in this study.

Results indicated that ethanol and carbon tetrachloride extracts of *Camellia sinensis* (I) can significantly decrease blood glucose in the diabetic group. In addition, the serum triglyceride level in the diabetic group treated with chloroform, carbon tetrachloride, or ethanolic extracts showed a significant reduction. For the total cholesterol, the diabetic group treated with ethanolic extract had a considerable reduction. Regarding HDL cholesterol, this factor was improved in the diabetic group treated with ethanolic extract. For LDL cholesterol, all of the extracts exclusive of essential oil were able to significantly decrease it. According to GC-MS tables and pharmacologic results, this effectiveness can be related to effective compounds in different extracts such as fatty acids, amides, and phenols besides its antioxidant, hypoglycemic, and hypolipidemic potential.

Our findings also indicated that some extracts of *Matricaria Chamomilla* (II) can significantly decrease blood glucose in the diabetic group. According to the research on diabetes induced by STZ in experimental animals, diabetes is caused by the irreparable loss of pancreatic beta cells, which leads to a decrease in insulin secretion. Also, diabetic animals with STZ may show more complications of diabetes, including cardiovascular, digestive, nervous, bladder, and kidney malfunctions during oxidative stress. The conducted research has stated various possible mechanisms regarding the effect of chamomile on the reduction of blood glucose, which can generally be divided into two types pancreatic and extra-pancreatic effects. Pancreatic effects refer to the factors which directly affect the production or secretion of insulin or cause an increase in insulin sensitivity. On the other hand, the compounds in chamomile may be indirectly effective on insulin secretion (34). According to the results obtained from GC/MS, there are anti-diabetic, antioxidant, anti-inflammatory, as well as anti-cancer compounds in the plant. Based on the studies, it has been proven that substances that have antioxidant and anti-inflammatory activity are effective for the management of diabetes (16).

The findings also illustrated that some extracts of *Carum Carvi* (III) can significantly reduce blood glucose in the diabetic group. The results obtained from GC-MS data indicate that different extracts of this plant are rich in terpene and fatty acid compounds. Various articles have mentioned the antidiabetic and cholesterol-lowering effects of terpene compounds in this plant (35). It seems that the effectiveness of some extracts of this plant is primarily due to the presence of terpene compounds as well as fatty acids. These extracts may decrease blood glucose levels through their effect on the islets of Langerhans of the pancreas and the stimulation of insulin secretion.

Conclusion

It is concluded that similar to many medicinal plants, polar and nonpolar organic as well as aqueous extracts of *Camellia Sinensis*, *Matricaria Chamomilla* and *Carum Carvi*, because of numerous effective compounds and less side effects than chemical medicines, could decrease blood sugar and rectify lipid factors in the diabetic experimental animals.

Collectively, it seems that predominant mechanisms for these activities may be targeting inflammatory cytokines, markedly decreased oxidative stress, or through insulin secretion which is concerned with their powerful bioactive constituents with various mechanisms of action and require further studies to explore it in the future.

Declarations

Author Contribution

A.S, A.A, M.R designed, planned the search strategy and protocol. S.B, N.F, N.A did the chemical and pharmacology experiments. All authors were responsible for original draft preparation. A.A, M.R and A.S edited the final manuscript. Each of the authors have confirmed the final version to be published and approved the conception of the study.

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Figures

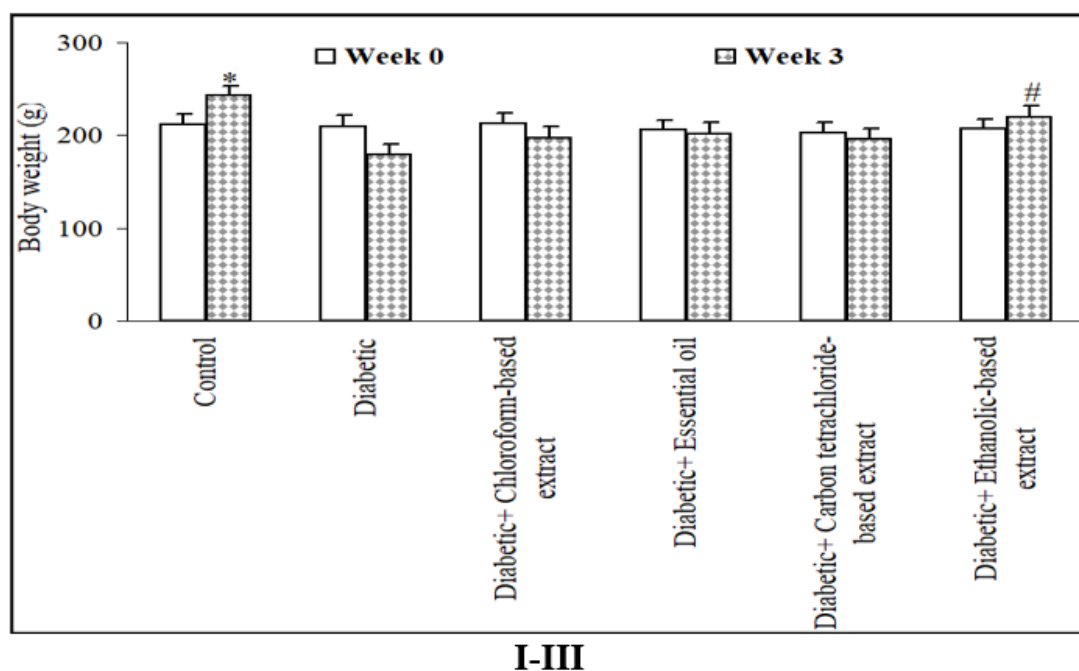


Figure 1

Body weight in various weeks in various groups receiving *Camellia Sinensis*, *Matricaria Chamomilla*, and *Carum Carvi* extracts (I-III) (means $\pm$ S.E.M). * $p < 0.05$ (as compared with control); # $p < 0.05$ (as compared with diabetic).

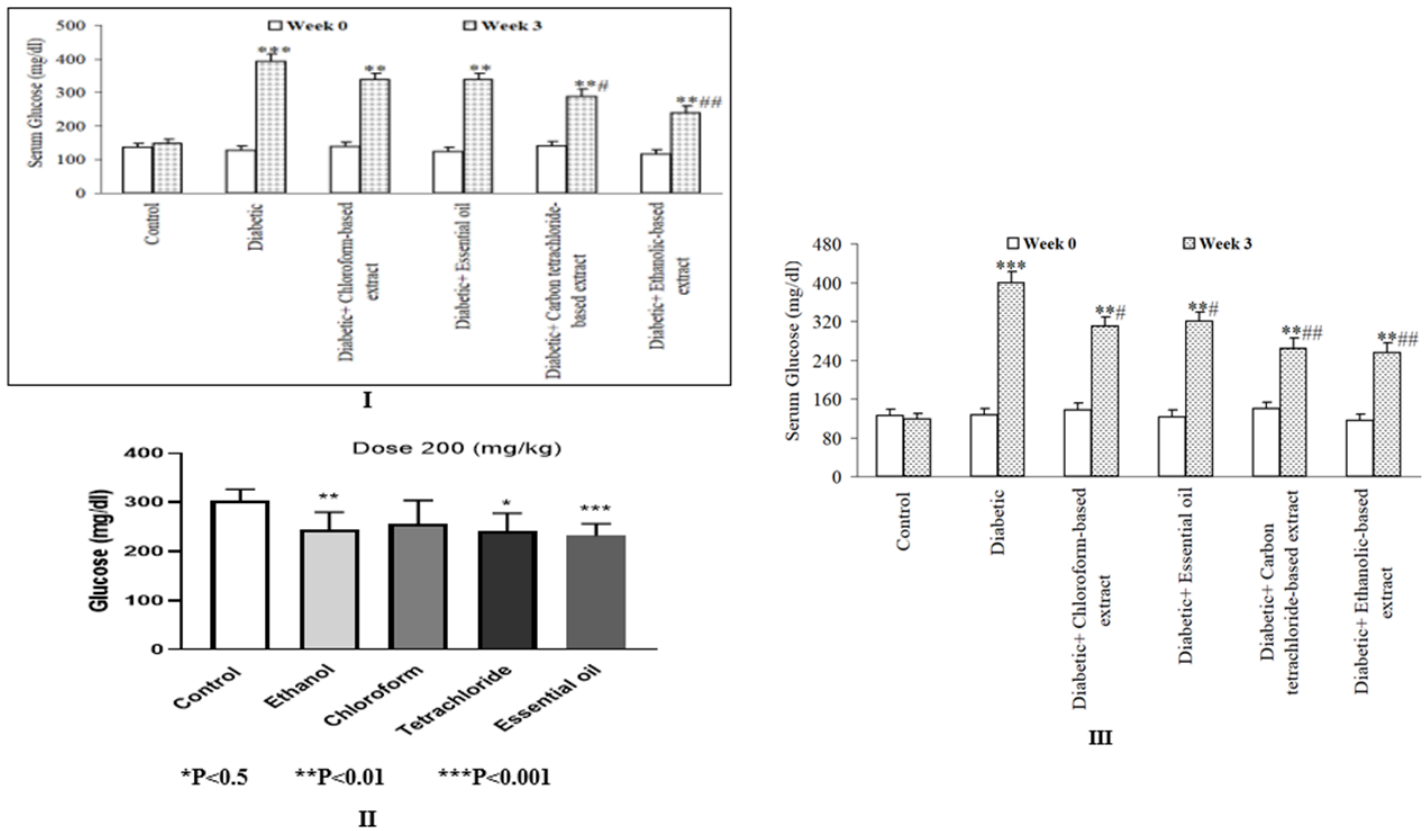


Figure 2

Serum glucose level in different weeks in different groups receiving *Camellia Sinensis*, *Matricaria Chamomilla*, and *Carum Carvi* extracts (I-III) (means $\pm$ S.E.M). * p<0.05, ** p<0.01, *** p<0.001 (as compared with the control); # p<0.05, ## p<0.01 (as compared with the diabetic).

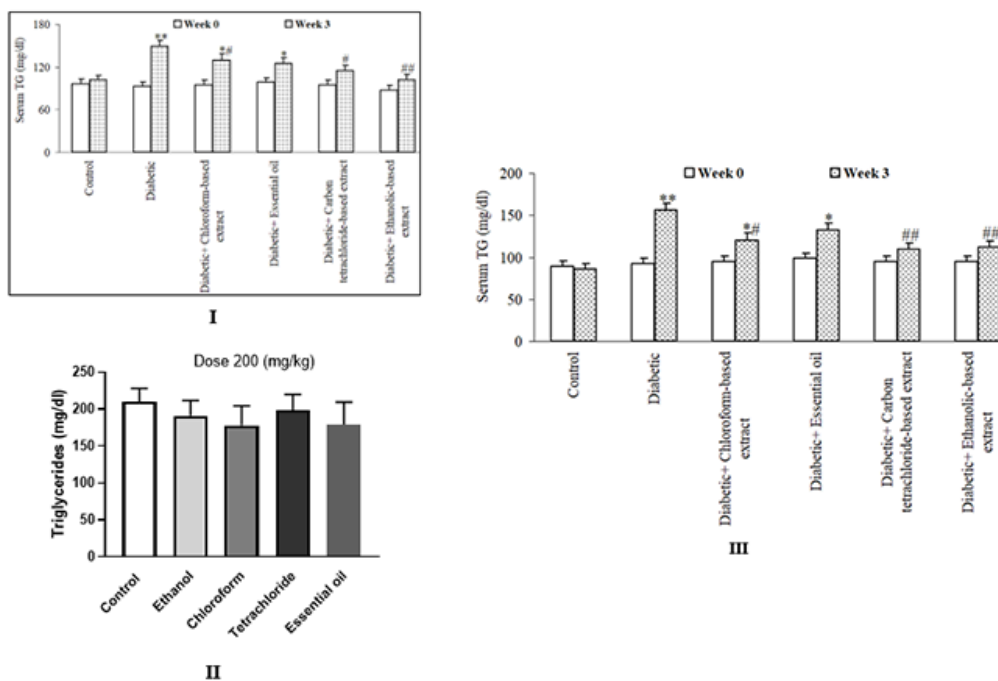


Figure 3

Serum triglyceride level in various weeks in various groups receiving *Camellia Sinensis*, *Matricaria Chamomilla*, and *Carum Carvi* extracts (I-III) (means $\pm$ S.E.M). * $p<0.05$, ** $p<0.01$, (as compared with control); # $p<0.05$, ## $p<0.01$ (as compared with diabetic).

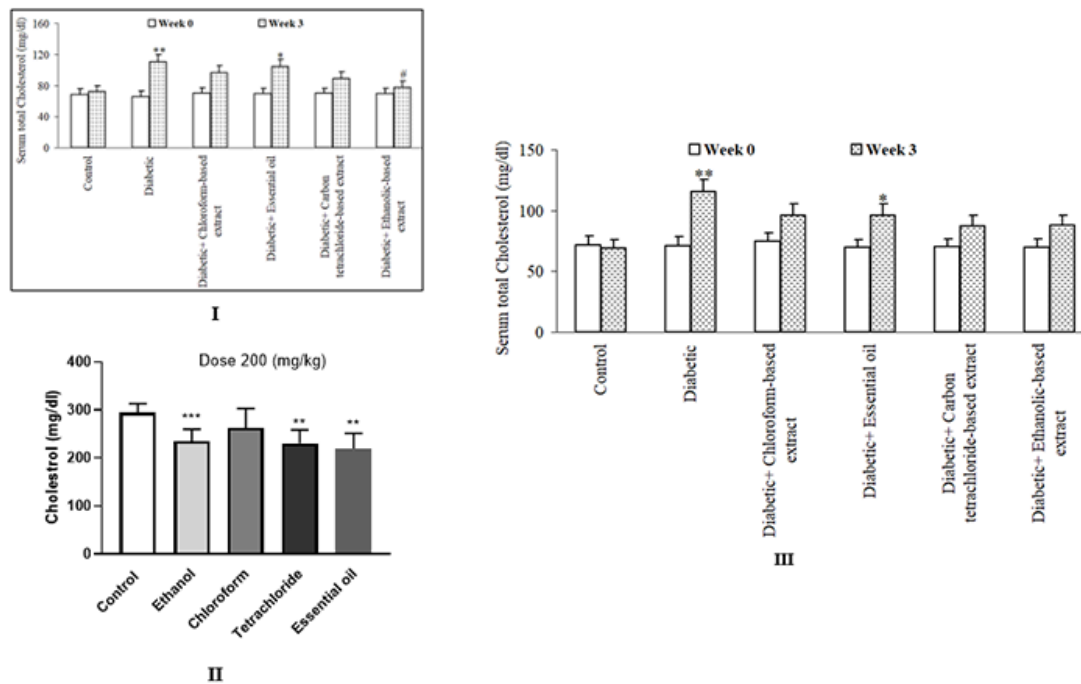
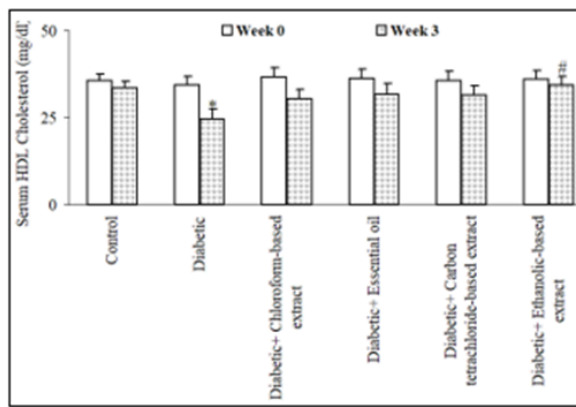
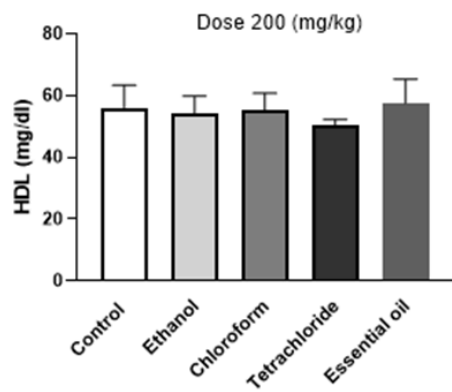


Figure 4

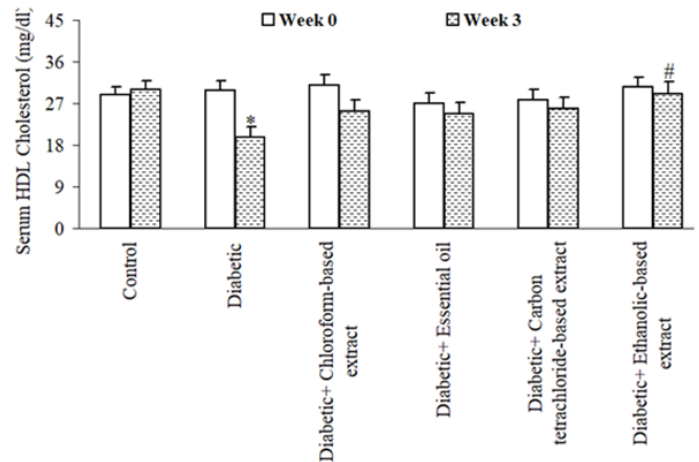
Serum total cholesterol level in various weeks in various groups receiving *Camellia Sinensis*, *Matricaria Chamomilla*, and *Carum Carvi* extracts (I-III) (means $\pm$ S.E.M). * $p<0.05$, ** $p<0.01$ (as compared with control), # $p<0.05$ (as compared with diabetic).



I



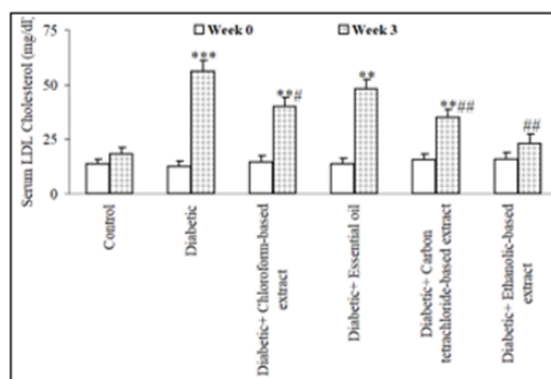
II



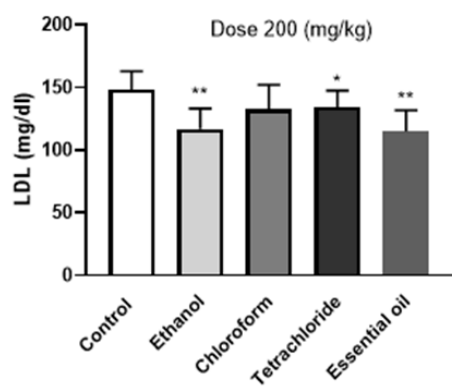
III

Figure 5

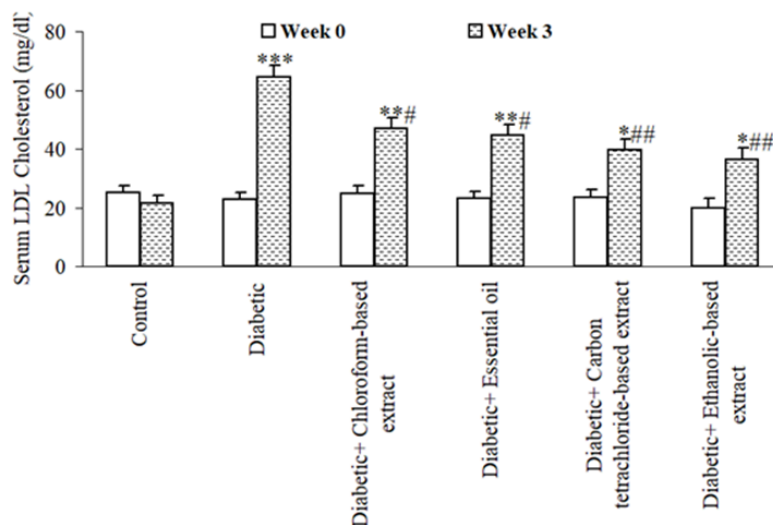
Serum HDL cholesterol level in various weeks in various groups receiving *Camellia Sinensis*, *Matricaria Chamomilla*, and *Carum Carvi* extracts (I-III) (means $\pm$ S.E.M). * $p < 0.05$, (as compared with control); # $p < 0.05$ (as compared with diabetic).



I



II



III

Figure 6

Serum LDL cholesterol level in various weeks in various groups receiving *Camellia Sinensis*, *Matricaria Chamomilla*, and *Carum Carvi* extracts (I-III) (means $\pm$ S.E.M). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ (as compared with control); # $p < 0.05$, ## $p < 0.01$ (as compared with diabetic).

Supplementary Files

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- [Presentation1.jpg](#)