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Original Research Article

Effect of Combined Administration of Ginger and Cinnamon on High Fat Diet induced Hyperlipidemia in Rats

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ABSTRACT

The present study was performed to further elucidate the hypolipidemic action of combined administration of ginger and cinnamon for their effects on the diet-induced hyperlipidemia in rats. It has been reported that plasma cholesterol and triglyceride concentrations decrease when animals are fed with mixture of ginger and cinnamon in 1% and 2% administration. Rats were fed cholesterol- free diet, (negative control), cholesterol-enriched diet and 5% of lard for 6 weeks. The study investigated the effects of combined administration of ginger and cinnamon at 1% and 2% adding on diet on triglyceride , total cholesterol, HDL-C and VLDL-C + LDL-C levels behinds effect of combined administration on AST and ALT enzymes , total protein and albumin concentrations . The results showed that combination of ginger and cinnamon could decrease levels of triglyceride (TG), total cholesterol (TC), very low density lipoprotein cholesterol + low density lipoprotein cholesterol (vLDL-C + LDL-C) and increase (HDL-C) in plasma (p<0.05). In addition ginger and cinnamon mixture decrease levels of AST and ALT enzymes but the level of total protein and albumin in plasma was unchanged (p<0.05).

Keyword: Ginger; cinnamon; triglycerides; cholesterol

INTRODUCTION

Cardio vascular diseases continue to be the leading causes of death in industrialized nations. Coronary heart diseases, reported to be the fifth leading cause of deaths in the year 1990 by WHO, are estimated to top the list by the year 2020. It is now well established that elevated levels of Cholesterol, Triglycerides, Low density Lipoprotein Cholesterol (LDL Cholesterol), Very low density Lipoprotein Cholesterol (VLDL Cholesterol) and decreased

levels of High Density Lipoprotein Cholesterol (HDL Cholesterol) are closely associated with coronary heart diseases and atherosclerosis. The clinical complications of atherosclerosis could be diminished and life to be prolonged when plasma lipid level was lowered by hypocholesterolemic agents [1]. But many promising agents developed have serious side effects, especially on adrenal function [2]**.** Many medicinal plants have been used in various traditional systems, for lipid management. Many kinds of Hypocholesterolemic activities from a lot of plant materials were confirmed till now [3,4]**.**

Zingiber officinale is a perennial plant commonly known as ginger. It has antibacterial and anti-inflammatory actions, and ginger rhizome is known to lower blood cholesterol level in man. Ginger rhizome is widely used as a spice or condiment. Ginger, a native perennial plant of Asia has been studied for its hypocholesterolemic and hypolipidemic effects [5,6]**.**

Cinnamon (*Cinnamomum zeylanicum*), has been used to treat diarrhoea and other problems of digestive system [7]**.** Cinnamon had traditionally been used to treat toothache and fight bad breath and its regular use is believed to stave off common cold and aid in digestion [8**].** Half teaspoon of cinnamon per day can lower LDL cholesterol [9]**.** Triglyceride and total cholesterol were decreased by administration of cinnamon extract in rats treated with streptozotocin for 3 weeks [10]**.** Cinnamon has shown an amazing ability to stop medication resistant yeast infections (www.herbwisdom.com). Smelling cinnamon boosts cognitive function and memory. It is a great source of manganese, fiber, iron and calcium [11]**.**

Therefore, objectives of this study were to evaluate the effect of combined administration of ginger root and cinnamon bark powder an supplementation as natural feed additives on hyperlipidemia rats.

MATERIALS AND METHODS

Cinnamon (Cinnamomum zillanicum), and ginger (Zingiber officinale) were obtained dry from a spices shop and milled.

Phytochemical screening:

Chemical test were carried out on the methanolic extracts using standard procedure to identify the constituents as described by [12,13].

Test for tannins:

1 g of each powdered sample was separately boiled with 20 ml distilled water for five minutes in a water bath and was filtered while hot. 1 ml of cool filtrate was distilled to 5 ml with distilled water and a few drops (2-3) of 10 % ferric chloride were observed for any formation of precipitates and any colour change. A bluish-black or brownish-green precipitate indicated the presence of tannins.

Test for saponins:

1 g of each powdered dried stain was separately boiled with 10ml of distilled water in a bottle bath for 10minutes. The mixture was filtered while hot and allowed to cool. The following test was then carried out.

Demonstration of frothing**:**

2.5 ml of filtrate was diluted to 10ml with distilled water and shaken vigorously for 2minutes (frothing indicated the presence of saponin in the filtrate).

Test for terpenoids:

5 ml of each extract was mixed in 2 ml of chloroform. 3 ml of concentrated H_2SO_4 was then added to form a layer. A reddish brown precipitate colouration at the interface formed indicated the presence of terpenoids.

Test for flavonoids:

1 g of the powdered dried of each specimen were boiled with 10 ml of distilled water for 5 minutes and filtered while hot. Few drops of 20 % sodium hydroxide solution were added to 1 ml of the cooled filtrate. A change to yellow colour which on addition of acid changed to colourless solution depicted the presence of flavonoids.

Test for alkaloids:

1 g of powdered sample of each specimen were separately boiled with water and 10 ml hydrochloric acid on a water bath and filtered. The pH of the filtrate was adjusted with ammonia to about 6-7. A very small quantity of the following reagents was added separately to about 0.5 ml of the filtrate in a different test tube and observed.

Picric acid solution.

10% tannic solution.

Mayer's reagent (Potassium mercuric iodide solution).

The test tubes were observed for coloured precipitates or turbidity.

Phenolic and flavonoids content:

Determination of total phenolic compounds:

A Folin- ciocalteu calorimetric method was used as described by [14]. To a 0.5 ml of (1mg/ml) extract a 2.5 ml of a ten-fold diluted Folin-ciocalteu reagent and 2 ml of 7.5%. Sodium carbonate solution were added before the reaction allowed standing for 30 min at room temperature. The absorbance was recorded at 760 nm by using spectrophotometer. The total phenolic compounds were determined according to gallic acid standard curve . The content of phenolic in extracts was expressed in terms of gallic acid equivalent (mg of GA / g of extract).

Estimation of total flavonoids

Aluminum chloride colorimetric method was used for flavonoids determination according to [15]. One milliliter (1 ml) of sample (1 mg/ml) was mixed with 3 ml of methanol, 0.2 ml of 10% aluminum chloride, 0.2 ml of 1 M potassium acetate and 5.6 ml of distilled water and remains at room temperature for 30 min. The absorbance of the reaction mixture was measured at 420 nm with UV visible spectrophotometer. The content was determined from extrapolation of calibration curve which was made by preparing rutin solution in distilled water. The content of flavonoids in extracts was expressed in terms of rutin equivalent (mg of RU / g of extract).

Reducing power :

The reducing power of different extracts was determined according to the method of Yen and Chen [16]. 2.5 ml of extract (25-800 µg/ml) in water were mixed with a phosphate buffer (2.5 ml, 0.2 M , pH 6.6) and potassium ferricyanide [$K_3Fe(CN)_6$] (2.5 ml, 1%). The mixture was incubated at 50^oC for 20 min. A portion (2.5 ml) of trichloroacetic acid (10%) was added to the mixture to stop the reaction, which was then centrifuged at 3000 rpm for 10 min. The upper layer of solution (2.5 ml) was mixed with distilled water (2.5 ml) and $FeCl_3$ (0.5 ml, 0.1%) and the absorbance was measured at 700 nm. Increased absorbance of the reaction mixture indicated increased reducing power.

Biological Evaluation

Animals

Adult male albino rats Sprague Dawely strain weighing between 90 – 100 gm , were obtained from the animal house of Egyptian Organization for biological Products and Vaccines (VACSERA) Cairo, Egypt. The animals study were taken after the prior approval of Animal Ethics Committee. The animals were kept in wire cages with wire bottom. The diet was introduced to the rats in special feed cup that kept food spilling to a minimum, water was provided to the rats by means of glass tube projecting through wire cage, an inverted bottle supported one side of the cage.

Experimental Design

Twenty rats were divided into four groups: group (A) control fed on basal diet, groups (B , C and D) were allowed to feed hyperlipidemic diet to induce hyperlipidemic through the feeding period. One of each experiment continued feeding hyperlipidemic diet without any supplementation saved as hyperlipidemic group (B) and the other two groups of each experiment were allowed to feed

hyperlipidemic diet with 1% mix of ginger and cinnamon powder as group (C) and 2% powder as group (D). Standard diet composition was described in (table 1) by [17] and hyperlipidemic diet was described by [18] as follows:

Table 1: Standard and hyperlipidemic diets

Ingredient	Standard diet	Hyper-lipidemic diet
Carbohydratesas starch	80 %	72.75 %
Protein as casein	10 %	10 %
Fats as corn oil	5 %	5 %
Salt mixture	4 %	4 %
Vitamins mixture	1 %	1 %
Cholesterol	0	2 %
Bile salts	0	0.25 %
Sheep tail fat	0	5 %

Blood sampling and analysis

Blood samples were collected after six weeks in tubes contain heparin as an anticoagulant from the eye plexuses under diethyl ether anesthesia and then centrifuged at 3000 rpm for 20 min. to obtain plasma, which was kept frozen until analysis. The total cholesterol was analyzed calorimetrically according to [19] method**.** HDL - cholesterol was determined according to [20] method**.** Acording to [21] plasma **V**LDL cholesterol plus LDL cholesterol was calculated as the difference between total cholesterol and HDL cholesterol . Risk ratio was calculated according the formula of [20] which Risk ratio = total cholesterol /HDL cholesterol . Atherogenic Index (AI) was calculated according to [22] using following equation:

$$\text{Atherogenic Index (AI)} = \frac{\text{Total cholesterol - HDL cholesterol}}{\text{HDL cholesterol}}$$

The triglycerides were analyzed according to [23] method. Alanine-aminotransferase (ALT) and aspartate-aminotransferase (AST) activities were measured according to the method described by [24] **.** Total protein was determined according to [25] method ., and albumin was determined according to [26] method.

Histopathology

Liver from the experimental groups were immediately fixed in 10% formalin, then treated with conventional grades of alcohol and xylol, embedded in paraffin and sectioned at 4–6 lm thickness. The sections were stained with Hematoxylin and Eosin (H&E) stain for studying the histopathological changes [27]**.**

Statistical Analysis

The results of the animal experiments were expressed as the Mean ± SE and they were analyzed statistically using the one-way analysis of variance ANOVA followed by Duncan's test. In all cases $p<0.05$ was used as the criterion of statistical significance.

RESULTS AND DISCUSSION

Phytochemical analysis

Phytochemical analysis is very useful in the evaluation of some active biological components of medicinal plants. The qualitative analyses was carried out in dry samples. Alkaloids, flavonoids, terpenoids, tannins, were revealed to be present in Cinnamon (Cinnamomum zillanicum), and ginger (Zingiber officinale) (Table 2) while saponins was absence . This shows high level of its possible medicinal and dietary values [28].

Table 2: The analysis of phytochemicals in the ginger and cinnamon:

Phytochemicals	Plants Ginger	Cinnamon
Alkaloids	+	+
Flavonoids	+	+
terpenoids	+	+
Tannins	+	+
Saponins	-	-

+ = presence; - = absence

A variety of herbs and herbal extracts contain different phytochemicals with biological activity

that can be of valuable therapeutic index. Much of the protective effect of fruits and vegetables has been attributed by phytochemicals, which are the non-nutrient plant compounds. Different phytochemicals have been found to possess a wide range of activities, which may help in protection against chronic diseases.

Total phenolic compounds and total flavonids in ginger and cinnamon extracts

Data in Table (3) showed that total phenolic content methanol ginger and cinnamon extracts were (266.7 and 331 mg gallic acid equivalent / g extract respectively). The total flavonoid of methanol and ginger and cinnamon extracts were (23.45 and 61.42 mg rutin equivalent / g extract respectively). Phenols and polyphenolic compounds, such as flavonoids, are widely found in food products derived from plant sources and they have been shown to possess significant antioxidant activities [29]. Studies have shown that increasing levels of flavonoids in the diet could decrease the occurrence of certain human diseases [30].

Table (3): total phenolic compounds and total flavonids in ginger and cinnamon extracts

Plant	Phenolic content (mg/g extract)	Flavonids content (mg/g extract)
Ginger	266.7	23.45
Cinnamon	331	61.425

Reducing power of ginger and cinnamon extracts

Fe (III) reduction is often used as an indicator of electron- donating activity, which is an important mechanism in phenolic antioxidant action [31]. In this assay, the presence of reductants (antioxidants) in the samples would result in the reduction of Fe^{+3} to Fe^{+2} by donating an electron. The amount of Fe^{+2} complex can be then be monitored by measuring the formation of Perl's Prussian blue at 700 nm. Increasing absorbance at 700 nm indicates an increase in reductive ability. Fig. 1 shows the dose– response curves for the reducing powers of the ginger and cinnamon methanol extracts It was found that the reducing powers of extracts also increased with an increase in their concentrations. At the highest concentration (200 µg/ml) of all tested materials cinnamon methanol extract showed higher activity (0.635) than ginger methanol extract (0.586). However, the inhibitory action of herb extracts could be enhanced by more recovery of phenolic compounds using suitable solvents because the connection of phenolics complex is not the same for all types of solvents used [32]. It can be concluded that the ginger methanol extract was considerably more effective as antioxidant in reducing power assay followed by cinnamon methanol extract.

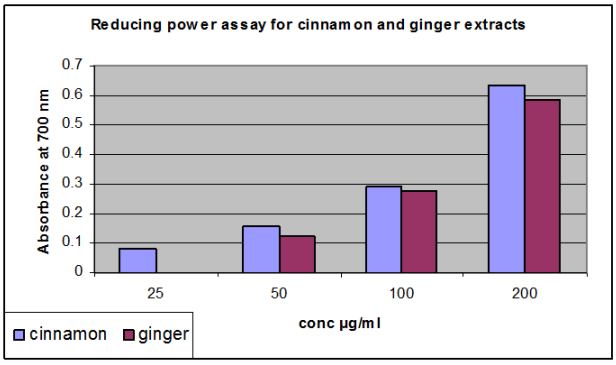


Fig. 1: Reducing power of cinnamon and ginger methanol extracts

Hyperlipidemia is a major contributor for health problems worldwide and leads especially to atherosclerosis, resulting in coronary heart diseases (CHD). According to WHO by 2020, 60% of the cardiovascular cases will be of Indian origin [33]. Hyperlipidemia induces the damages in various tissues, which in turn, alters the cellular functions leading to cell damage and many pathological conditions [34]. A high-fat diet may cause elevated levels of cholesterol, which ultimately leads to obesity. Elevated cholesterol level particularly LDL, VLDL increases the risk of cardiovascular diseases particularly coronary heart disease (CHD) [35] .

Increase in HDL cholesterol reduces the risk of CHD [36,37]**.** Reduction of 1% cholesterol can lead to 2-3% reduction of CHD risk [38] .The high fat diet (HFD) administered in present study for effective hyperlipidemia. induction. The significant ($p<0.05$) change in lipid profile noticed in the experimental animals confirmed the induction of hyperlipidemia in HFD fed rats (Tables 4 and 5). High fat diet increased triglycerides level and leads to hardening of arteries [39,40]. The present study showed that HFD significantly ($p<0.05$) increased TG level when compared with standard pellet treated rats. Treatment with ginger: cinnamon at the different dose levels (1% and 2% adding on HFD) for 30 days showed significant ($p<0.05$) decrease in triglyceride and total cholesterol levels in hyperlipidemic rats compared to positive control. HDL is a beneficial lipoprotein synthesized in intestine and liver which protects the system from the pathogenesis of atherosclerosis [41]. In the present study, it is noticed that HDL cholesterol level in plasma increased significantly ($p<0.05$) in ginger : cinnamon mixture treated hyperlipidemic rats.(26.94 and 22.26 mg/dl for 1% and 2% mixture adding on high fat diet respectively compared with positive control 15.73 mg/dl.

Table 4: Ttotal cholesterol , triglycerides and HDL-C (mg/dl) in rats fed hyperlipidemia induced diets with different levels of ginger : cinnamon mixture in diet.

Group / Parameter	Total cholesterol mg/dl	Triglyceride mg/dl	HDL-C mg/dl
Negative control	56.48±2.91 [a]	57.28±1.2 [a]	31.92± 0.49 [d]
Positive control	110.48±1.27 [d]	96.58±1.17 [d]	15.73± 0.59 [a]
Ginger : Cinnamon 1%	74.68± 0.77 [b]	63.81± 0.32 [b]	26.94± 0.58 [c]
Ginger : Cinnamon 2%	82.41± 1.03 [c]	85.47± 0.48 [c]	22.26± 0.45 [b]

Each value is the mean ± SD. Means have different superscript letters indicate significant variation at ($P \leq 0.05$), while the same letters indicate non significant variation.

Increase in LDL level causes deposition of cholesterol in the arteries and aorta and hence is a leads to CHD. LDL transports cholesterol from the liver to the periphery [42, 43]. The fortification of LDL from oxidation and decrease in oxidative stress might therefore be useful for prevention of atherosclerosis associated CVD. In the present study administration of combined administration of ginger and cinnamon at two different dose levels effectively reduced VLDL cholesterol plus LDL cholesterol content of hyperlipidemic rats. For a good lipid lowering therapy, a drug should be able to significantly lower LDL and increase HDL cholesterol concentration and this appreciably decreases the fatty cytoplasmic vaculated cells in liver parenchyma and prevents hepatic necrosis and this correlates with the present study [44]. Reduced VLDL + LDL and increased HDL concentration were observed in the present study, thereby suggesting that this formulation could be used as a good lipid lowering therapeutic agent. Atherogenic index (AI) signifies the deposition as foam cells, plaque or fatty infiltration in circulatory system. An increased atherogenic index indicates high risk of susceptibility of heart and kidney to oxidative damage [45].

Table 5: LDL-C mg/dl , risk ratio and atherogenic index AI , in rats fed hyperlipidemia induced diets with different levels of ginger : cinnamon mixture in diet.

Group / Parameter	VLDL-C + LDL-C mg/dl	Risk ratio	Atherogenic index
Negative control	24.56± 2.45 [a]	1.77± 0.23 [a]	0.77± 0.06 [a]
Positive control	94.75± 1.76 [d]	10.2± 0.36 [d]	9.3± 0.65 [d]
Ginger : Cinnamon 1%	47.74± 1.28 [b]	4.1± 0.16 [b]	1.77± 0.09 [b]
Ginger : Cinnamon 2%	60.14± 0.94 [c]	5.49± 0.24 [c]	2.69± 0.06 [c]

Each value is the mean ± SD. Means have different superscript letters indicate significant variation at ($P \leq 0.05$), while the same letters indicate non significant variation.

In the present study, treatment with combined administration of ginger and cinnamon at the dose of 1% and 2% on HFD indicated significant ($p<0.05$) decrease in atherogenic index compared with positive control , thus indicating the protective role of test formulation against atherogenesis.

Positive control group showed significant ($P<0.05$) increase of serum lipid profile parameters (TC, TG, VLDL-C + LDL-C) compared to those of negative control group . This finding indicates that HFD that is used to elevate the serum lipid profile parameters was able to elevate all parameters except HDL-C measured in this experiment. Similar study done by [46] supports the present study.

Cinnamon might have a direct role in lipid metabolism and prevent hypercholesterolemia and hypertriglyceridemia and lower free fatty acids by its strong lipolytic activity. Dietary cinnamate inhibits the hepatic HMG Co-A reductase activity (a key enzyme involved in regulating cholesterol metabolism and decrease serum total cholesterol level) resulting in lower hepatic cholesterol content and suppresses lipid peroxidation via enhancement of hepatic antioxidant enzyme activity [47]. *Cinnamomum cassia* may have an effect on treating hyperlipidemia and thereby may be responsible for the prevention of consequences of the aging process, from hypertension to heart failure, cardiovascular diseases and myocardial infarction. Therefore, further studies could establish the effect of *Cinnamomum cassia* on hyperlipidemic human beings.

Ginger is now considered much existing interest for its potential to treat many aspects of cardiovascular disease. Reviews of the more recent trials, suggest that ginger shows considerable anti-inflammatory, antioxidant, anti-platelet, hypotensive and hypolipidemic effect *in vitro* and animal studies [48].

[49] studied the effect of aqueous extract of *Z.officinale* on plasma cholesterol concentration in cholesterol-induced albino rats. They found that, *Z.officinale* revealed a statistically significant ($P<0.05$) decrease in plasma cholesterol in comparison with the control group. There are several mechanisms by which plant products may lower cholesterol and triglyceride levels, either by increase removal of VLDL by peripheral tissues [50] or increased excretion of bile in the feces [51**.** 52] interpreted that the *Z.officinale* (Zanjabeel) is documented as good hypolipidaemic natural agent as well as antioxidant natural agents. Z.*officinale* (Zanjabeel) was found to be significant in lowering the level of serum TG and serum VLDL-cholesterol in patients of primary hyperlipidaemia. The proposed mechanisms in various studies done so far for this effect of ginger are as follows:

1. It inhibits the hydroxymethylglutaryl Co A (HMG-Co A) reductase [53] which is a rate limiting enzyme for cholesterol biosynthesis (like that of statins).

2. It promotes excretion and impairs absorption of cholesterol [53].

It increases the activity of 7- alphahydroxylase, the rate limiting enzyme in the catabolic conversion of cholesterol to bile acids in liver [54, 55].

Despite the aforementioned studies on mechanism of lowering the cholesterol levels by ginger more studies are needed for the confirmation, that is, whether only one or more of the aforementioned proposed mechanisms are associated with decrease in lipid levels.

Table 6 presents the results of plasma AST and ALT activities in the controls and experimental groups. There were significant increases ($P < 0.05$) in the plasma AST, and ALT activities of hyperlipidemic rats as compared to normal control rats . The present finding are in agreement with those obtained by [56] who found that hypercholesterolemia state significantly stimulate ALT and AST activity in the plasma. Significant decrease ($P < 0.05$) in plasma AST and ALT activity of rats fed hyperlipidemia-induced diet which feed diet containing ginger : cinnamon mixture, at doses 1% and 2% compared to hyperlipidemia control . In the study, it was observed that as a result of hyperlipidemia, enzymes such as AST and ALT were released into blood. Their increase in the plasma activities of these enzymes was directly proportional to the degree of cellular damage. These values decreased by combined administration of ginger and cinnamon.

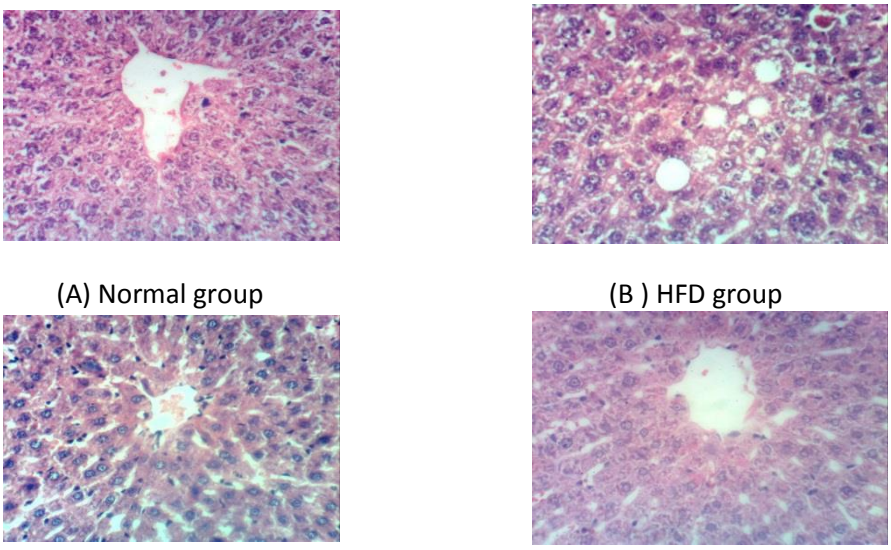
No changes in total protein and albumin content were observed by chitosan groups when compared with hyperlipidemia control group.

Table 6: Plasma AST and ALT activities , total protein mg/dl and albumin mg/l in rats fed hyperlipidemia induced diets with different levels of ginger : cinnamon mixture in diet.

Group / Parameter	AST (U/L)	ALT (U/L)	Total protein	Albumin
Negative control	92.43± 2.24 ^{a}	61.96± 0.99 ^{a}	6.99± 0.23 ^{a}	3.38± 0.35 ^{a}
Positive control	122.9± 2.79 ^{d}	81.46± 0.23 ^{c}	6.75± 0.68 ^{a}	2.97± 0.24 ^{a}
Ginger : Cinnamon 1%	101.6± 1.11 ^{b}	62.4± 0.62 ^{a}	7.3± 0.22 ^{a}	3.74± 0.66 ^{a}
Ginger : Cinnamon 2%	105.35± 1.24 ^{c}	65.63± 1.4 ^{b}	7.4± 0.27 ^{a}	3.11± 0.7 ^{a}

Each value is the mean ± SD. Means have different superscript letters indicate significant variation at ($P \leq 0.05$), while the same letters indicate non significant variation.

Fig.2 presents the histopathological observation of liver revealed the accumulation of triglycerides and fatty changes. Groups (A, C and D) showing no histopathological changes ,while group (B) high fat diet showing fatty change of hepatocytes. The administration of ginger: cinnamon mixture at 1% and 2% reversed the pathological changes and brought back the normalarchitecture of the liver.



(A) Normal group (B) HFD group

(C) Ginger : Cinnamon 1% (D) Ginger : Cinnamon 2%

Fig. 2: Histopathological changes detected in the liver of (A) normal group, (B) HFD group, (C) Ginger : Cinnamon at 1% and (D) Ginger : Cinnamon at 2%.

CONCLUSION

To sum up, the effect of combined administration of ginger and cinnamon was studied in experimental rats, where hyperlipidemia was induced through high fat diet. The administration of mixture to the hyperlipidemic rats significantly reduced total cholesterol, TG, and VLDL + LDL .The combined administration of ginger and cinnamon revealed maximum protective effect at a dose 1% on HFD in comparison with 2% . Further in-depth studies can result in the development of an effective combined administration of ginger and cinnamon as anti-obesity drug.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

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