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Ultrastructural Evaluation of the Antihyperlipidemic Effect of Combined Administration of Cinnamon and Ginger on the Salivary Glands of Hypercholesterolemic Rats

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Abstract

Hypercholesterolemia is characterized by elevated blood cholesterol levels, which are treated with synthetic medications like statins. Plant extracts like ginger and cinnamon can lower blood triglycerides and total cholesterol while increasing HDL cholesterol. Studies show that cinnamon and ginger increase high-density lipoprotein cholesterol and decrease blood triglycerides and total cholesterol. The current study aims to assess the antihyperlipidemic impact of administering ginger and cinnamon together on hypercholesterolemic rats' salivary gland.

Keywords: Ginger, Cinnamon, Submandibular Salivary Gland, Hypercholesterolemia.

Full length article *Corresponding Author, e-mail: asmaaahmedfoad14@gmail.com

1. Introduction

Fat, a term in nutrition, biology, and chemistry, refers to triglycerides, a common ester of fatty acids, and lipids, which are biologically relevant substances soluble in non-polar solvents but insoluble in water [1]. It has been hypothesized that a high-fat diet is detrimental to your health. According to [2], high calorie consumption and inactivity are contributing to an increase in the global prevalence of dyslipidemia. By substituting fish oil for portion of the saturated fat, the HFD totally counteracted the lipogenic effects of saturated fat and avoided diet-induced hepatic steatosis. Cinnamon is a plant that has a variety of uses among many different cultures, from spicing up foods to deterring germs from growing [3]. According to [4], cinnamon extract reduces hyperlipidemia by presumably directly influencing lipid metabolism through the inhibition of hepatic β-hydroxy β-methylglutaryl-CoA (HMG-CoA) reductase activity. This lowers the amount of cholesterol produced in the liver and suppresses lipid peroxidation. Commonly used herbs and spices like garlic, black cumin, cloves, cinnamon, thyme, five spices, bay leaves, mustard, and rosemary have been shown in an increasing amount of studies to have antibacterial qualities and may even be utilized therapeutically [5]. It was discovered that giving mice cinnamon improved their lipid profile by lowering the amounts of triglycerides and high density lipoproteins (HDL) in their serum. Moreover, elevated HDL levels may result from enhanced lecithin cholesterol acyl transferase (LCAT) activity, which is crucial for blood lipid

homeostasis. One possible explanation for the lower triglyceride levels could be cinnamon's lipolytic activity. Furthermore, it is possible that the maintenance of a low level of triglycerides is due to the suppression of triglyceride production [6]. It was stated that items made from plants have been utilized for medical purposes for hundreds of years. Approximately 80% of people on the planet today are thought to rely on herbal remedies to treat their medical conditions. In phytotherapy, which uses plants and their chemical components to treat specific health issues, spices and herbs are frequently used. The rhizomes of ginger (Zingiber officinale Rosc.) and mulberry (Morus indica L.) leaves are two examples of herbs that have drawn attention from researchers due to their hypolipidemic qualities and potential use as helpful adjuncts in lowering the risk of coronary artery disease when combined with current medication [7]. Ginger works as a hypolipidemic agent in cholesterol-fed rabbits. Ginger has been demonstrated to dramatically lower serum total cholesterol and triglycerides while increasing high-density lipoprotein (HDL) cholesterol levels when compared to pathogenic diabetic rats [8]. It has been proposed that an aqueous extract of ginger may limit intestinal absorption of dietary fat by inhibiting its breakdown. On the other hand, one clinical investigation found that ginger had no effect on blood lipid and sugar levels, but there have been no good clinical studies of ginger's lipid-lowering effect [9].

2. Materials and Methods

2.1 Materials preparation

2.1.1 Preparation of Cholesterol Rich Diet

Cholesterol rich diet was prepared by mixing, cholesterol (10gr), casein (120gr), salt mixture (50gr), vitamin mixture (10gr), soybean oil (250gr), choline (0.4gr), cellulose (130gr) and corn starch (429.6gr), bile salt mixture (2.5gr) necessary for intestinal absorption of cholesterol [10].

2.1.2 Preparation of Ginger

Dried powder was obtained from (Harraz) local market in Cairo for herbs, it dissolved in distilled water in a concentration of 10% and administrated by oropharyngeal tube [11].

2.1.3 Preparation of Cinnamon

Dried powder was obtained from (Harraz) local market in Cairo for herbs, it was dissolved in distilled water in a concentration of 10% and administrated by oropharyngeal tube [12].

2.2 Methods

2.2.1 Sample Size Calculation

The sample size will be calculated using G* Power version 3.19.2, Franze Faul, University Kiel, Germany. Copyright © 1992-2014. The effect size 0.8 using both (α) and beta (β) level of 0.05, i.e., power = 95%; the estimated sample size (n) should be at least 60 rats for 6 groups, 7 rats in each group.

2.3 Study Design

21 adult male albino rats with body weight 160- 180 gm each at the beginning of the experiment.
Rats were acclimated for 7 days before the experimentation. They were housed under good ventilation in separate cage (5 rats each). Adequate suitable diet consisting of fresh vegetables, dried bread and tap water was available ad libitum throughout the experimental period.
This was done under supervision of specialized animal caretaker since their housing till termination which was done by the incinerator.

2.4 Animals Grouping and Treatment Protocol

Rats were equally divided into two main groups as follow:

2.4.1 Control group

For four months, seven rats from this group were fed a regular meal and given distilled water via a stomach tube.

2.4.2 Experimental groups

2.4.2.1 Cholesterol-rich diet group

For four months, the seven rats in this group were fed a diet high in cholesterol that included 1% powdered cholesterol [13].

2.4.2.2 Cholesterol-rich diet + Ginger+ Cinnamon group

Seven rats in this group were given a diet high in cholesterol for a period of four months. at the beginning of the fourth month, the administration of both cinnamon and ginger powder was initiated at a dose of 6 gm \ kg. BW and 100 mg \ kg. BW, respectively, for a duration of one month [14].
-Lipid profiles were measured before and after hypercholesterolemia induction (at the end of the third month), as well as at the end of the study period.
-Rats were individually slaughtered by cervical dislocation at the conclusion of the four months, and the submandibular salivary gland was extracted from their skulls right away. Under a light microscope, specimens were prepared for regular histological and ultrastructural analysis.

3. Results

3.1 Biochemical Analysis: Table, 1, (Fig. 1)

Mean Plasma Cholesterol level before induction of hypercholesterolemia, at the end of the third month and at the end of the fourth month in all groups revealed:
Consistent levels, with the control group having lower cholesterol levels. After the fourth month, the cholesterol group had significantly higher mean cholesterol levels. The Cholesterol+ Ginger+ Cinnamon group showed a significant drop in

cholesterol levels, but no significant difference was found between the groups. Table (1), (Fig.1 A, B, C).

3.2 Histological Results: (Fig. 2)

3.2.1 Control group

The parenchyma of the submandibular gland is made up of granular convoluted tubules, collecting ducts, and secretory end pieces. The secretory terminal sections are composed of serous cells with a pyramidal shape and highly basophilic nuclei. The cuboidal cells in intercalated ducts have nuclei at the base and a tiny lumen. The striated ducts are characterized by numerous basal striations and columnar cells with open-faced nuclei positioned centrally. Excretory ducts have a wide lumen and columnar cells that have been pseudostratified (Fig 2: A, B).

3.2.2 Cholesterol-Rich Diet group

2-Cholesterol-Rich Diet group: A four-month research on rats given a high-fat diet showed anomalies in the submandibular salivary gland. A hyper fibrotic capsule with many cytoplasmic vacuoles divided the gland lobes. Blood cells that had extravasated and were kept in the major excretory duct were observed. Boundaries inside the acinar cells were disturbed, and there were indications of vacuolar degeneration in the cytoplasm. Some nuclei displayed aberrant mitosis, and others had conspicuous chromatin. The design of the intercalated duct was atypical, featuring low cuboidal cells and poorly defined cell borders. The granular convoluted tubules displayed a necrotic appearance, and the cells lost their characteristic architectural pattern. Striated duct cells lost all basal striations and exhibited poorly defined cell borders. Red blood cells that had extravasated were seen in dilated blood arteries (Fig 2: C, D).

3.2.3 Cholesterol Rich Diet+ Ginger+ Cinnamon Group

Microscopic analysis of submandibular salivary gland sections stained with haematoxylin and eosin in rats given 100 g/kg BW plus 6 mg/kg BW for a month showed that the gland's normal structural characteristics were mostly maintained. This was demonstrated by the maintenance of the characteristic acinar appearance and the distinctly normal arrangement of secretory cells in acini with a spherical shape. The gland's parenchyma revealed the appearance of serous acini, which had pyramidal cells and a nucleus positioned basally. Additionally, cellular boundaries were covered. Acinar cells' cytoplasm was seen to be basophilic. A narrow lumen containing cuboidal cells with a typically appearing nucleus was seen in the intercalated duct. The cellular borders of striated ducts exhibited regeneration (Fig. 2: E, F).

3.3 Ultrastructural Results: (Fig. 3)

3.3.1 Control Group

The submandibular salivary gland of the control group had normal ultrastructural elements when examined under an electron microscope. The rat's submandibular salivary gland's serous acini had a spherical appearance with a central, narrow lumen surrounded by massive pyramidal cells. The nucleus of every cell was spherical and situated basally. The secretory cells' cell organelles were all arrayed in the same way as they would be in any seromucous gland: several parallel arrays of rough endoplasmic reticulum (RER), randomly distributed mitochondria with their distinctive cisterna, and basally and laterally positioned Golgi bodies. The cytoplasm's apical region is filled with a large number of secretory granules that vary in size and electron density. Different electron densities of free ribosomes and lysosomes were detected. The granular convoluted tubules were lined by tall columnar cells with large rounded, basally located nuclei. A lot of well circumscribed apically located membrane bound granules with various electron densities were observed Numerous desmosomal junctions and lateral interdigitation between the adjacent cells were noticed. The basal part of the cells contained rounded euchromatic nuclei surrounded by numerous mitochondria (Fig. 3: A, B).

3.3.2 Cholesterol-Rich Diet Group

The cholesterol-rich diet group's submandibular salivary glands showed severe ultrastructural abnormalities, including atrophic changes in serous secretory cells and pyramid-shaped acinar cells with erratically arranged nuclei, including shrunken nuclei, on electron microscopical examination. Secretory cells were found in irregular acini with a small lumen, exhibiting significant organelle degeneration and damaged mitochondria. Most parenchymal components had significant cytoplasm vacuolization. Reduced desmosomes led to a broader intercellular connection, with reduced desmosomes resulting in no interdigitation. Granular convoluted tubules were significantly affected, with numerous cell vacuolization in duct cells. Granule quantity, pleomorphic forms, sizes, and electron dense concentrations decreased. (Fig.3: C, D).

3.3.3 Cholesterol-Rich Diet+ Ginger+ Cinnamon Group

The submandibular salivary gland of the ginger+ cinnamon treated group was examined under an electron microscope, which revealed: Large pyramidal cells with a rounded nucleus basally situated were observed in the serous acini cells of the rat's submandibular salivary gland. There were free ribosomes and mitochondria arranged randomly throughout the acinar cells. Lateral interdigitation was also seen. Adjacent cells' cell membranes displayed strong intercellular connections, which were indicated by a large number of integrations and desmosomes. Granular convoluted tubules were lined by tall columnar cells with large rounded, basally located nuclei. A lot of well circumscribed apically located membrane bound granules with various electron

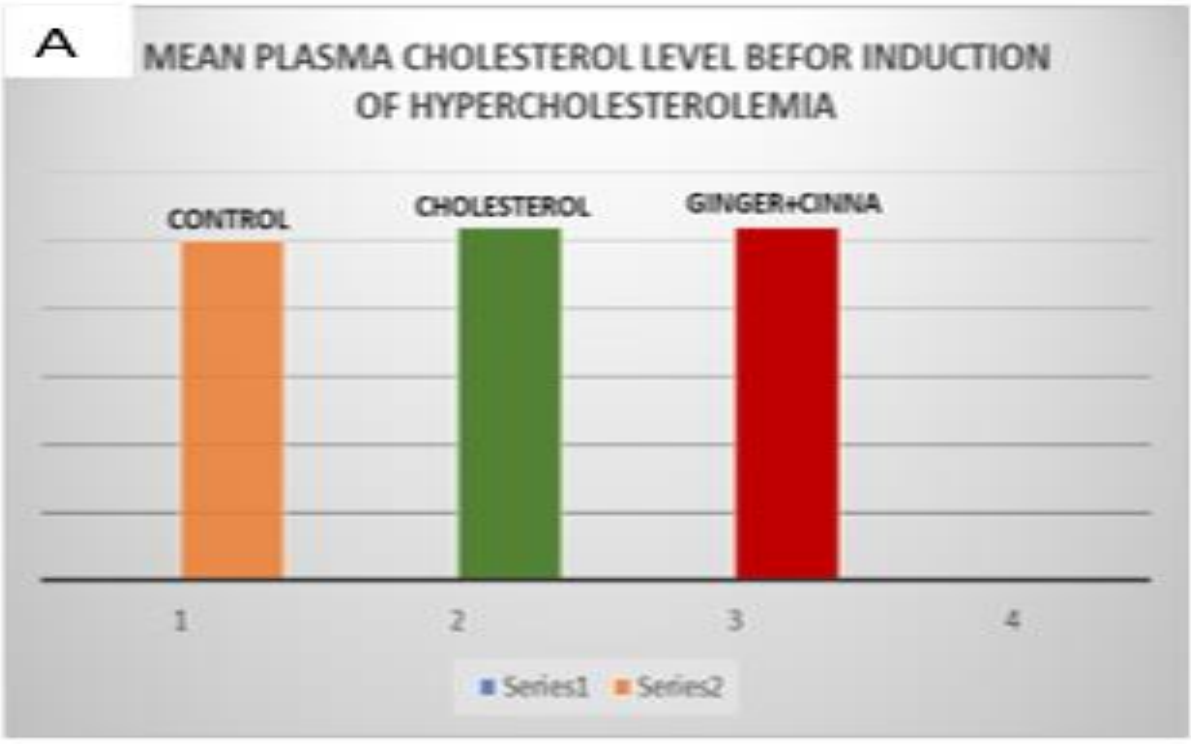
densities were observed, scattered mitochondria and free ribosomes were observed around the nucleus Numerous desmosomal junctions and lateral interdigitation between the adjacent cells were noticed (Fig: 3 E, F).

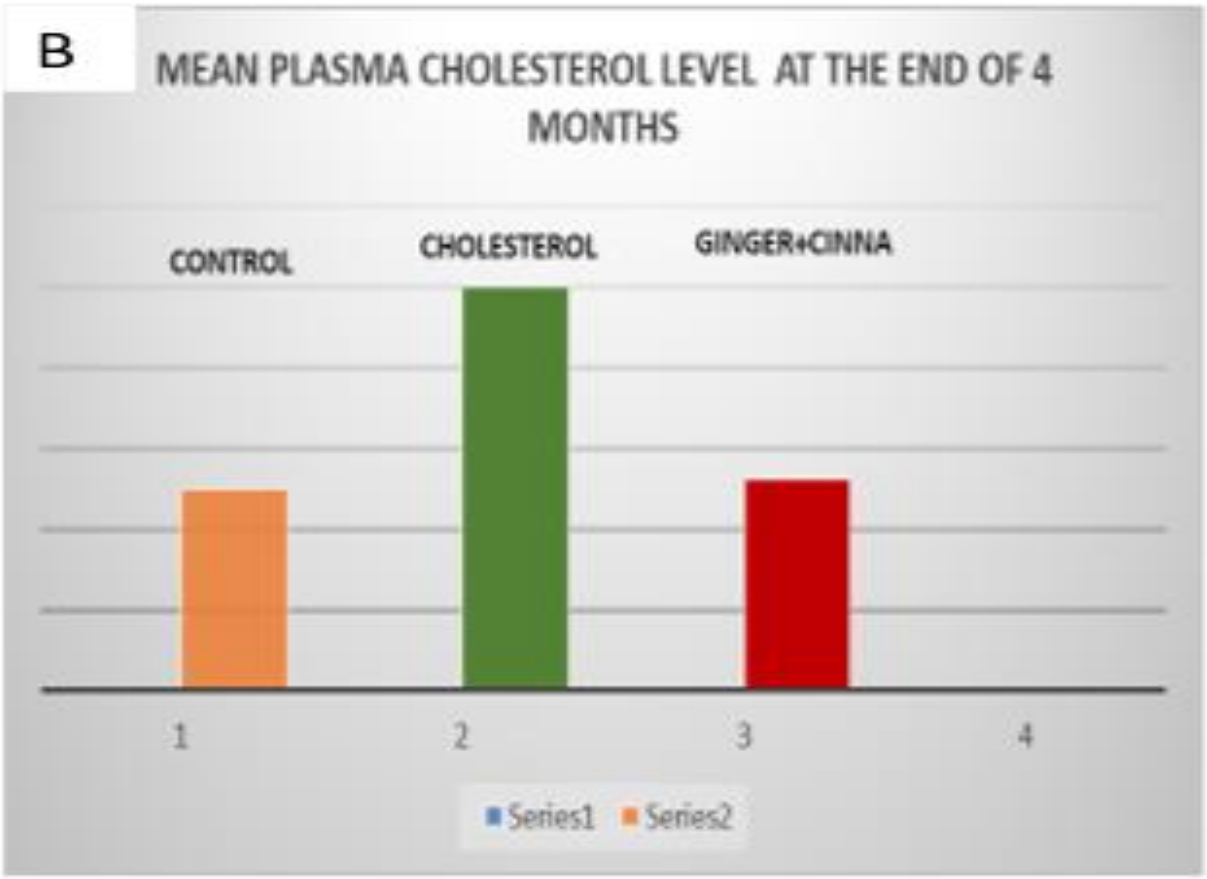
4. Discussion

According to research, albino rats' high-fat diet and cholesterol crystals cause hypercholesterolemia and obesity, which suggests that the rodents could serve as human obesity models [15]. Excess lipids are retained as droplets in the cytoplasm of salivary gland secretory cells when intake surpasses initial consumption [16]. When cholesterol crystals were given to the albino rats in the diet group that was high in cholesterol, the result was hypercholesterolemia, which raised cholesterol levels significantly. This result is in line with previous research by [17], who employed albino rats fed different kinds and amounts of fats and found that the plasma lipid profile increased. Research suggests that nutrition plays a major role in the development of atherosclerosis and hyperlipidemia. In both humans and animals, saturated fatty acids and cholesterol raise total cholesterol and change lipoprotein patterns, resulting in hypercholesterolemia. In animal models, feeding cholesterol has been utilized to induce hypercholesterolemia and anomalies in metabolism [18]. The current study found that a high-cholesterol dietary supplement was sufficient to induce hyperlipidemia. According to [19], similar outcomes were shown in rats and rabbits on a high-cholesterol diet. Higher serum lipid profile markers were also seen in these investigations. Rats given a high-fat diet were used in the study to assess their lipid profiles. It was discovered that plasma cholesterol and LDL had significantly increased while HDL had decreased. This is consistent with earlier studies showing elevated levels of triglycerides, cholesterol, total lipids, and LDL in response to a hyperlipidemic diet [20]. Moreover, [21] found that a hyperlipidemic diet led to a considerable decrease in HDL, a large increase in total cholesterol, and LDL with a minor increase in the rats' weight. These data corroborate our statistical findings. Additionally, it has been proven that dietary fat and cholesterol regulate the expression of the apolipoprotein gene and the lipoprotein response, which in turn causes fluctuations in plasma cholesterol concentrations. After four months of feeding a high-fat diet, the submandibular salivary gland of albino rats was investigated histologically and ultrastructural. This demonstrated that the high-fat diet altered the histological structure of the submandibular salivary gland and caused the acinar cells to lose their typical morphological pattern. A high-fat diet causes major alterations in the parotid salivary gland, which limits the flow of oxygen and nutrients and causes inflammation, according to studies by [22]. The survival and functionality of the parenchymal cells may suffer as a result. Furthermore, intracellular lipids generate a large number of vacuoles that may be connected to fatty degeneration, leading to degenerative alterations that mainly affect the fatty nature of secretory cells. Studies reveal that a diet heavy in fat causes lipids to accumulate in secretory cells, particularly in the salivary glands. Excess lipids accumulate as droplets in salivary gland cells when intake of lipids surpasses consumption; this strain on acini borders causes damaged and distorted boundaries [23]. According to the study, apoptosis, or cell death, is caused by severe vacuolation in mammalian cells and is typified by thick cytoplasm. In order to make up for this, the cell expands and vacuolates, making its membrane more permeable. Apoptotic cells usually have autophagic or lipid-filled vacuoles, which suggest that degeneration is occurring. The Golgi apparatus and endoplasmic reticulum may be impacted by hypotonic shock expansion, which increases mitochondrial permeability and causes cytoplasmic vacuolization, an adaptive physiological response to avoid harm [24]. Rough endoplasmic reticulum (RER) enlargement is also explained by Takashi et al. (2005), who reported that RER enlargement is associated with a cellular state that precedes the indications of apoptosis.

The researchers clarified that hypercholesterolemia's effect on ATP oxidation and phosphorylation was the source of the substantial changes that may lead to the breakdown and rupture of mitochondria. In this group, there were also preserved examples of ruptured and destroyed mitochondria with lost cisternae. Moreover, the production of ATP via the Kreps cycle and oxidative phosphorylation of ATP are the two main functions of the mitochondria. increased cholesterol affecting ATP, which affects how cells function [26]. According to Knight et al. (2002), lipid problems aggravate mitochondrial damage caused by oxidative stress, hence increasing the risk of atherosclerosis. An explanation for ruptured mitochondria and their destruction along with the loss of their cisternae was also provided by earlier research that showed that the most important targets of harmful stimuli are mitochondria, which are the sites of ATP generation, and cell membranes, which are required for maintaining the ionic and osmotic homeostasis of the cell and its organelles. They claimed that the primary causes of ATP depletion are reduced availability of oxygen and nutrients, damage to mitochondria, and the impact of certain substances [28]. In the meanwhile, Miller and James (2017) reported to have discovered signs of cytoplasmic vacuoles, which are portions of the endoplasmic reticulum that have expanded and been pinched off (also known as hydropic or vacuolar degeneration). These vacuoles caused cellular swelling, which is the first indication of cell injury. Since a number of mitochondria are packed between basal infoldings of the plasma membrane, causing the basal striations of striated duct cells, as demonstrated by electron microscopic studies [30]. Our study's discovery of the loss of these basal striations may be related to oxidative stress-induced mitochondrial

damage. In this study, albino rats given a high-fat diet for four months were also given ginger and cinnamon. As is evident, the outcomes were favorable. When the submandibular salivary gland of hypercholesterolemic rats was studied under a microscope, both histologically and ultrastructurally, the typical structural features of the gland were largely intact. The preservation of the duct cells' and the acini's typical morphology, along with the clearly visible normal arrangement of secretory cells in the spherically formed acini, served as evidence for this. The results presented above were consistent with those of Shalaby and Sahfan and El Rokh et al. (2010), who found that obese rats administered cinnamon and ginger for four weeks had lower total cholesterol (TC) and triglycrides (TG) than the positive control group [31, 32]. In addition to the previously reported findings, a further investigation revealed that a blend of cinnamon and ginger has higher concentrations of antioxidant-rich active ingredients (zingerone, 4-hydroxyiso flavone, chlorogenic acid, catachin, caffein, and sinapic acid), as well as cinnamic acid and querectin. When compared to the cholesterol group, the results of the tests performed on this group's blood showed a significant decrease in low-density lipoprotein and cholesterol as well as high-density lipoprotein. Current statistical data showed a significant increase in high density lipoproteins, which is in line with previous studies that found that feeding ginger and cinnamon combined dramatically reduced the levels of LDL and total cholesterol in rats with hyperlipidaemia [32]. According to Mahmoud et al. (2022), adding ginger and cinnamon at varying doses to the diet of hyperlipidaemic rats led to a large rise in high-density lipoproteins and a significant decrease in total triglycerides, cholesterol, and low-density lipoproteins. Histological changes in liver cells were also lessened by this decrease in lipid buildup in the cells [33]. According to earlier research, rats fed a high-fat diet for four months had decreased blood levels of cholesterol and low density lipoprotein after taking a half-teaspoon of cinnamon daily [34]. Ginger administered concurrently has been shown in numerous studies to considerably lower serum levels of triglycerides, HDL cholesterol, LDL cholesterol, and total cholesterol. This implies that ginger modulates cholesterol metabolism and turnover in a beneficial way [35]. Through a variety of processes, including interfering with the liver's ability to produce cholesterol and disturbing the GI tract's absorption of cholesterol, ginger has the potential to lower plasma lipid levels [36]. Ginger has been shown to have antioxidant effects that influence hypocholesterolaemia and are anti-atherogenic. These traits may be related to the regulation of HMG-CoA reductase activity and the inhibition of LDL oxidation [37]. The liver enzyme reduction seen while utilizing these components may be due to the antioxidant qualities of cinnamon's cinnamic acid and zingerone, a catechin present in ginger extract, according to research by Roussel et al. (2009) and Abdel-Azeem et al. (2013). When butter was added, mice's ALT enzyme activity was significantly reduced [38,39, 40].





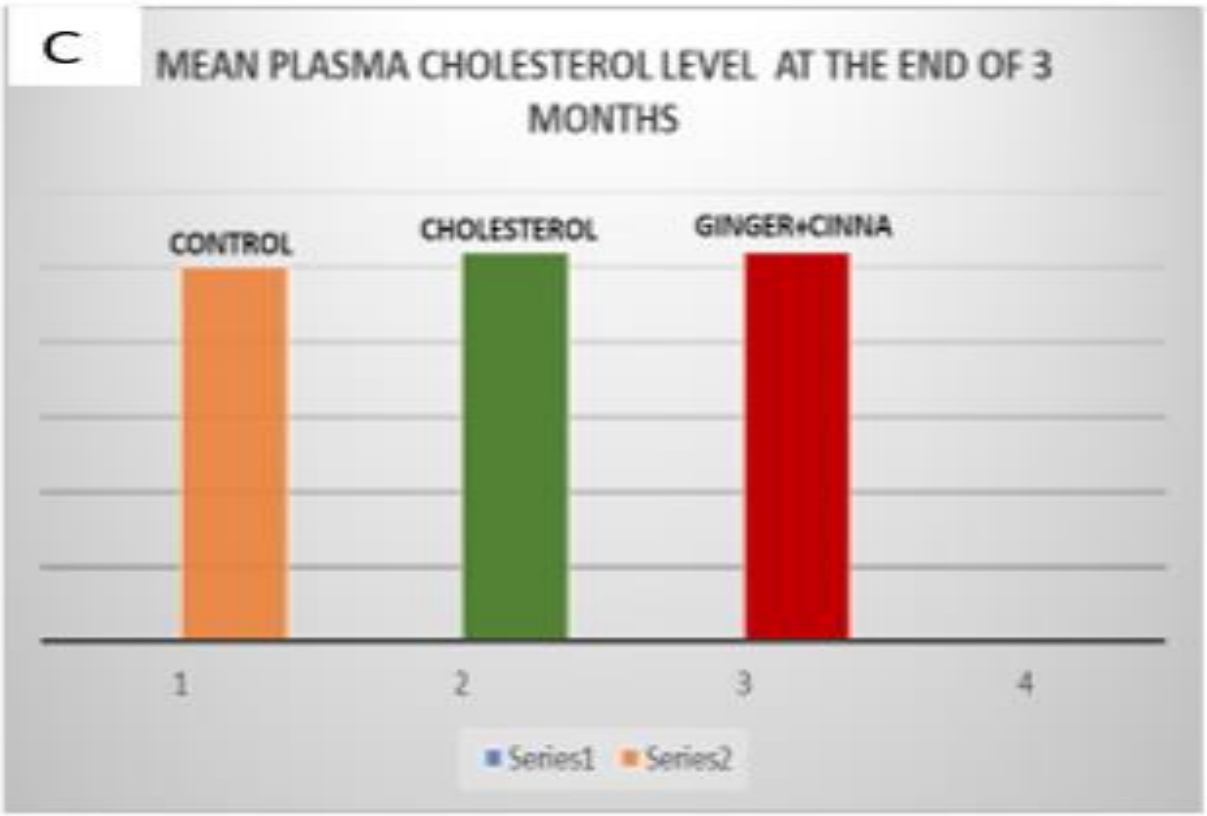


Figure 1: Before hypercholesterolemia induction, at the end of the third month, and at the end of the fourth month, for each group, the mean plasma cholesterol levels are displayed.

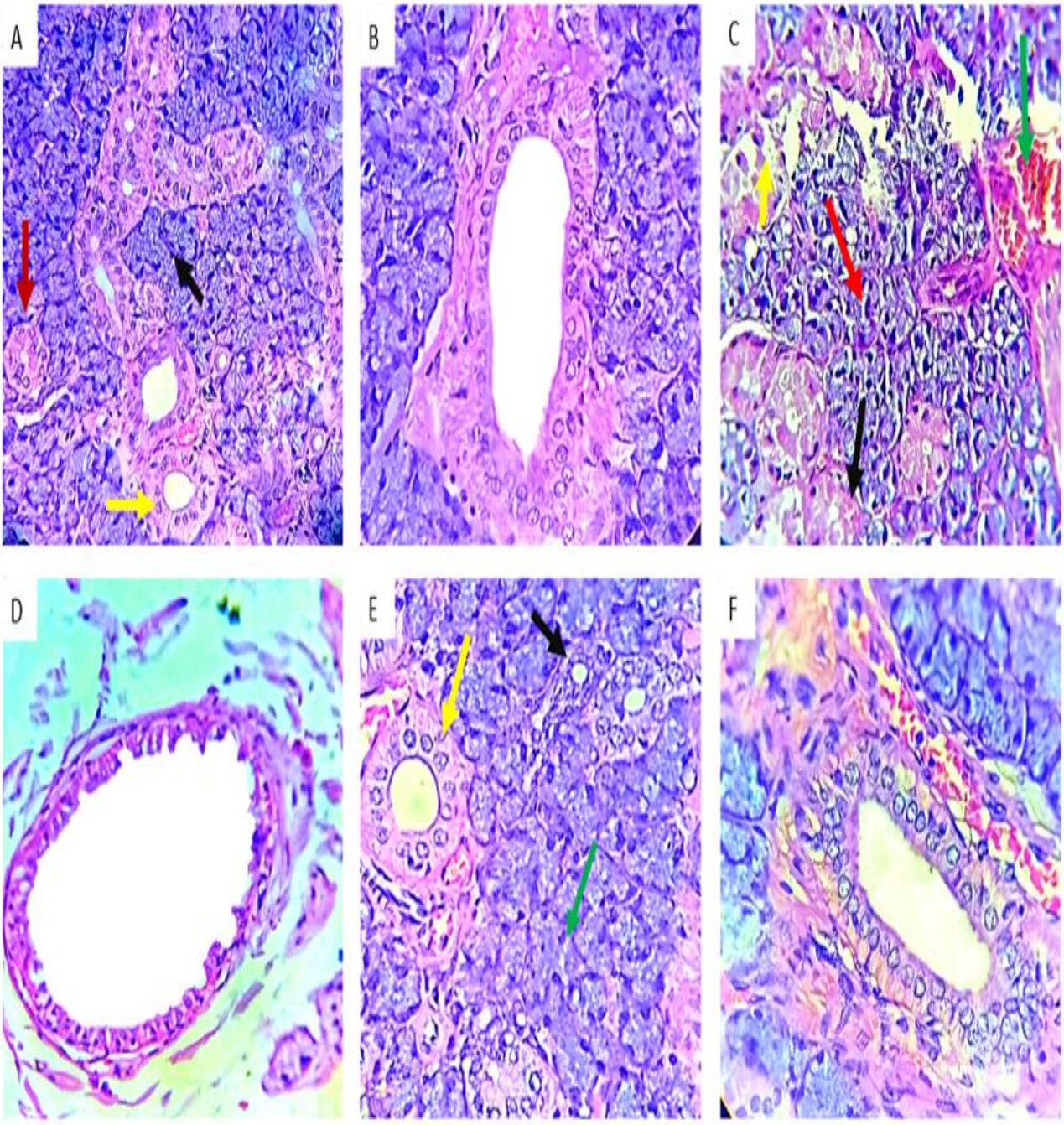


Figure 2: (A): A photomicrograph showing serous acini (black arrows) in the control group. Intercalated channels are indicated by red arrows, while striated ducts are indicated by yellow arrows. (B): The control group's photomicrograph showed a pseudostratified excretory duct. (C): A photomicrograph of the cholesterol group showing a serous acinus with vacuolated cytoplasm, a wide lumen, and a convoluted tubule with necrotic cells (yellow arrow). A green arrow indicates a dilated blood artery obstructed by red blood cells, whereas black arrows indicate vacuum-separated striated ducts devoid of basal striation. (D): A photomicrograph showing the excretory duct's lack of pseudo stratification, taken from the same group. (E): A photomicrograph showing the ginger+ cinnamon treated group's regular spherical acini (green arrow). The intercalated duct (black) and the striated duct with basal striations (yellow arrows) (H& E org. mag, 640).

Table 1: showing mean plasma level before induction of hypercholesterolemia, at the end of third month, at the end of the fourth month

	Mean of plasma level before induction of hypercholesterolemia	Mean Plasma Cholesterol level at the end of the third month	Mean Plasma Cholesterol level at the end of the fourth month
Control	97.432	98.857	99.125
Cholesterol rich diet	97.28	165.542	233.525
Cholesterol+ Cinnamon+ Ginger	98.251	168.221	99.284

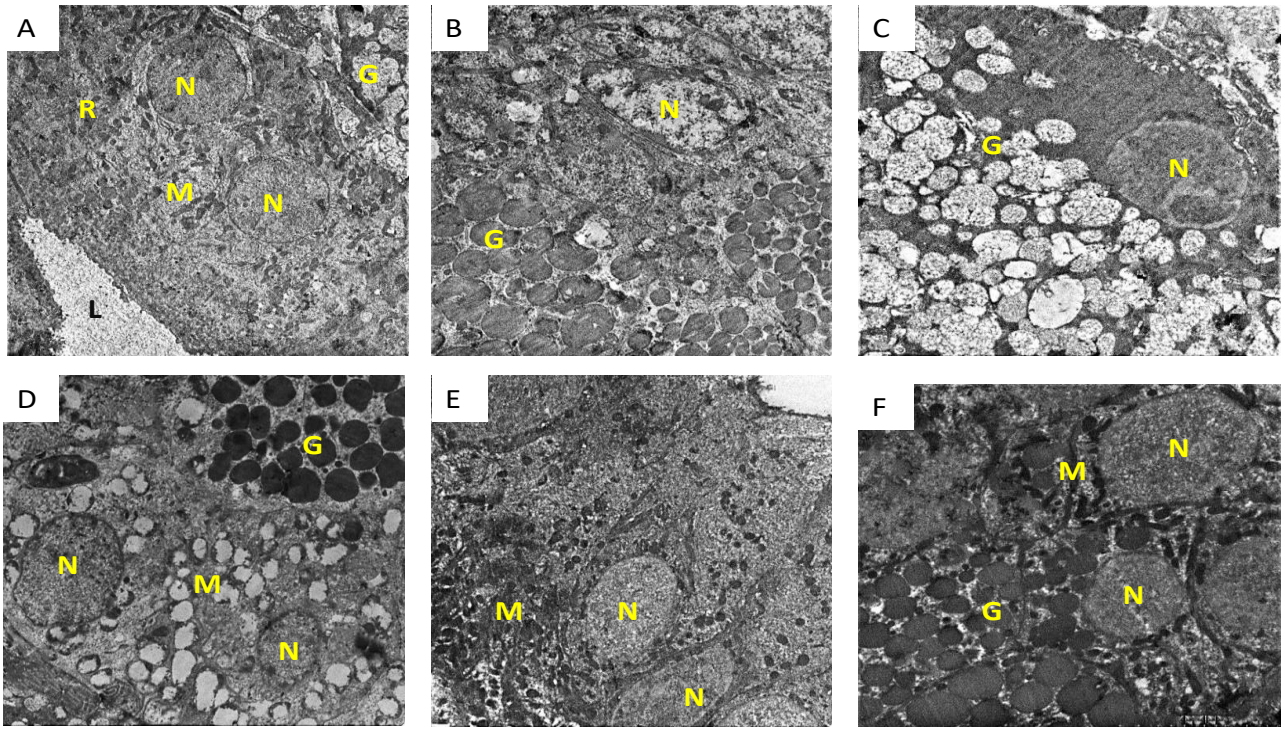


Figure 3: (A): Electron micrographs of the control group displaying serous acinar cells with free ribosomes (R), secretory granules (G), and rounded basally located nuclei (N). (B): An electron image of the same group demonstrates the cytoplasmic granules (G) and granular convoluted tubule rounded nuclei (N). We saw lateral interdigitations (I) (lead citrate x 12000 & urean acetate). (C): Electron microscopy of the cholesterol group revealed several cytoplasmic vacuoles (V) (Uranyl acetate & lead citrate x 12000), an irregularly shaped nucleus (N), and total degradation of cytoplasmic organelles. (D):): Electron microscopy of Cholesterol group exhibited granular convoluted tubule with considerable decrease in quantity of granular contents (G). Degenerated nucleus (N) and burset mitochondria (M.(E): An electron micrograph of the group treated with cinnamon and ginger demonstrating acinar cells) (Uranyl acetate & lead citrate x 12000).

Rats given a mixture of 100 mg ginger and 100 mg cinnamon did not exhibit any histological changes in their liver cells, according to a similar result by Mahmoud et al. (2022) [41]. Hassanen (2010) found in earlier investigations that rats fed ginger, and cinnamon had less abnormal liver histology [42]. Another study by Mousa et al. (2021) discovered that treating rats with ginger enhanced the livers' histological features [43]. Mixed extracts of ginger and cinnamon, administered at 1% and 2% of the diet to hyperlipidaemic rats, had the strongest protective impact on liver cells and acted as anti-obesity drugs, according to Salah and Moustafa (2016) [44].

5. Conclusion

Based on previous studies that used ginger and cinnamon separately to treat high cholesterol, these herbs were combined to combat the destructive effect of high cholesterol and to see the extent to which gland tissue improves when combined.in this study we concluded that hypercholesterolemia adversely damages the submandibular salivary glands. in rats with elevated cholesterol. The anatomy of the submandibular glands and blood cholesterol levels responded well to ginger+ Cinnamon administration. The tissues and blood cholesterol levels responded well to the administration of the herbals as a line of treatment for hypercholesterolemia.

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Data Availability Statement

Not applicable.

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Corresponding authors extend her appreciation to her professors.

Conflict of interest

Thers is no conflict of interest between authors.

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