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The Effects of Atorvastatin, Ginger, and Cinnamon on the Structure of Rats' Submandibular Salivary Gland Fed on Cholesterol-Rich Diet

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Abstract: Hypercholesterolemia is a term used to describe high amounts of cholesterol in the blood. The statin family of substances, a heterogeneous collection of molecules that impede the action of HMG CoA reductase, is one of the most important synthetic pharmaceuticals used to address such disorders. Plant extracts are increasingly being utilized to treat a variety of diseases. According to studies, Cinnamon and ginger lowers blood triglycerides and total cholesterol while increasing HDL cholesterol, or high-density lipoprotein.

Aim of the Study: The present study's goal was to compare the effect of statin (Atorvastatin) and Herbals (Ginger+ Cinnamon) on the submandibular salivary gland of hypercholesterolemic albino rats.

Materials and Methods**:** There were two groups of 40 mature male albino rats. **(1) Control group:** rats were kept on a normal diet, **(2) Experimental groups**: Hypercholesterolemic group: rats fed with hypercholesterolemic rich diet for 4 months, Atorvastatin and Cinnamon+ Ginger groups: rats were given Atorvastatin tablets and Cinnamon+ Ginger powder at the beginning of the third month with a dose of 10 mg/kg BW. and 6 gm \Kg. BW+ 100 mg\ Kg. BW respectively. Sections 5 mm thick of the parotid gland were examined histologically, ultra-structurally, and immunologically by anti-Caspase Ⅲ immune antibody.

Results: The high cholesterol group had significant degenerative alterations in the parenchymal parts of the submandibular salivary gland, whereas the Atorvastatin and Cinnamon+ Ginger groups demonstrated significant enhancing effects in the histological structure of the rat's submandibular gland.

Conclusion: To varying degrees, hypercholesterolemia wreaks havoc on the anatomy of the parotid gland. The use of Atorvastatin as a synthetic line of treatment for hypercholesterolemia improved submandibular gland tissue and blood cholesterol levels. Cinnamon+ Ginger administration improved submandibular gland tissue as a natural herbal remedy for high cholesterol levels in the blood.

Key Words: Submandibular Salivary Gland, Cinnamon, Ginger, Atorvastatin, Hypercholesterolemia.

Introduction

One of the lipids, cholesterol, is vital for maintaining the fluidity and biophysical properties of cellular membranes by decreasing permeability and increasing compactness. Cholesterol is necessary for embryonic and fetal development. Furthermore, cholesterol includes bioactive molecules that can influence cellular metabolism as well as intracellular and extracellular communication, such as steroid hormones, vitamin D, and bile acids. **(Woollett 2011).**

There are several treatment options for hypercholesterolemia, including natural treatments and pharmaceutical drugs. Statins are among the most important synthetic drugs used to treat such medical conditions because they constitute a heterogeneous group and inhibit the action of HMG CoA reductase (hydroxy methyl glutaryl coenzyme A), an essential enzyme for the creation of cholesterol. As a result, statins are used to treat dyslipidemia all over the world **(Nayor and Vasan 2016)**.

Atorvastatin is one of the statins recommended for the treatment of dyslipidemias such as primary hyperlipidemia and mixed dyslipidemia in adults, hypertriglyceridemia, primary lipoproteinemia, homozygous familial hypercholesterolemia, and heterozygous familial hypercholesterolemia in adolescents who have failed to respond to dietary changes **(Qiu, Zhuo et al. 2017)**.

Many Indonesians frequently use plant-based traditional medicine. One of these species is Cinnamomum burmannii, a kind of cinnamon. It significantly reduces blood sugar levels. It has the potential to be anti-diabetic because to the large amounts of cinnamaldehyde it contains. Cinnamon is hypothesized to directly alter lipid metabolism due to its significant lipolytic action, avoiding hypercholesterolemia, hypertriglyceridemia, and the formation of free fatty acids. Cinnamaldehyde, the most abundant chemical in Ceylon cinnamon bark extracts, has been demonstrated in vitro to mildly inhibit bile acid binding, cholesterol micellization, and cholesterol esterase. Because of its function in bile acid synthesis, it may lower cholesterol levels **(Heydarpour, Hemati et al. 2020)**.

Plant extracts are now often used to treat a wide range of ailments. According to research, ginger significantly decreases total cholesterol and triglycerides while increasing high-density lipoprotein (HDL) cholesterol levels, serving as a hypolipidemic agent **(Lie et al.,2003).**

Materials and Methods

Before the present study could begin, the Faculty of Dentistry at Suez Canal University's Research Ethics Committee (REC) approved it with permission number (284/2020). According to the sample size estimate, the study included 28 male mature albino rats. In addition to ethical issues, experimental animal care protocols were followed. A pledge form for animal care was given to (REC) Appendix.

Twenty eight adult male albino rats (weighing between 200-250 gm each) were used in this study. The animals were separated into the following categories:

1- **Control group.** 7 rats were kept on a normal diet and received distilled water via a gastric tube for 4 months.
2- **Experimental groups: 2-A Cholesterol-rich diet group:** This group consisted of 7 rats and received a cholesterol-rich diet containing 1% cholesterol for 4 months **(Moubarak 2008)**.

2-B Cholesterol-rich diet + Atorvastatin group: This group of 7 rats was fed a cholesterol-rich diet for three months before starting Atorvastatin at the beginning of the fourth month in conjunction with a cholesterol diet at a dose of 10 mg/kg body weight until the end of the testing period **(Ulicna, Vancova et al. 2012)**.

2-C Cholesterol rich diet + Cinnamon+ Ginger group: This group included 7 rats that were fed a high-cholesterol diet for four months. Cinnamon and ginger powder administration was initiated at the beginning of the fourth month at a dose of 6 gm Kg. BW+ 100 mg Kg. BW for one month **(Salah, 2015).**

Blood samples were taken from each rat at the start of the trial, three months later, and at the completion of the experiment in all groups. Lipid profiles were evaluated before hypercholesterolemia was induced, after hypercholesterolemia was induced (at the end of the third month), and after the trial period. After four months, the rats were slain. Their heads were promptly dissected after cervical dislocation to extract the submandibular salivary gland. Under a light microscope, specimens were processed for regular histological and histochemical testing.

Results:

I- Biochemical Analysis:

- **Mean Plasma Cholesterol level before induction of hypercholesterolemia, all groups' results after the third month and the fourth month showed:** Before induction of hypercholesterolemia, plasma cholesterol levels were the same in all groups, and the t-test revealed no statistically significant difference between groups.
- The mean plasma cholesterol level following hypercholesterolemia induction was lower in the control group compared to the other groups.
- At the conclusion of the fourth month, the average plasma cholesterol level in the cholesterol group was considerably higher than in the other groups.
- The cholesterol + Atorvastatin group showed a significant decline when compared to the Cholesterol group; however, there was no difference between the Cholesterol+ Atorvastatin group and the Control group.
- When compared to the Cholesterol group, the Cholesterol+ Cinnamon+ Ginger group exhibited a significant reduction, but when compared to the control group, there was no noticeable difference (Figs. 1A, B, C) and Table (1).

II- Histological Results:

1- Control group: H&E-stained sections indicated that the submandibular gland parenchyma was morphologically constituted of secretory terminal pieces and collecting ducts. The intercalated duct has a small lumen and cuboidal cells with nuclei at the base. The striated ducts were made up of columnar cells with open-faced nuclei in the center and a lot of basal striation **(Fig. 2A).** Excretory ducts exhibited prominent pseudostratefication of columnar cells and a broad lumen **(Fig. 2B).**

2- Cholesterol-rich diet group: This group's microscopic investigation revealed a lack of the normal morphological pattern of acinar cell organization in typical spherical acini. The acinar cells' borders were disturbed. Their cytoplasm exhibited vacuolar degeneration. The nuclei had substantial chromatin, and some acinar cell nuclei showed evidence of aberrant mitosis. The architecture of the intercalated duct was aberrant, with ill-defined cell borders. Striated duct cells emerged, with ill-defined cell borders and no basal striations. The cytoplasm seemed

deteriorated, and the majority of the nuclei showed symptoms of necrosis with vacuolated cytoplasm **(Fig. 2C).** The excretory duct exhibited pseudo stratification loss, cytoplasmic vacuoles, and extravasated blood in the duct lumen **(Fig. 2D).**

3- **Cholesterol-rich diet+ Atorvastatin:** Histological analysis of this group revealed a restoration to normal acinar morphology with distinct normal organization of secretory cells into spherical-shaped acini. Some of the serous acini had fully burst cells. Some acinar cells were discovered to have lost their regular pyramidal form and cellular borders. Normal cell borders were seen in the intercalated duct, which had a limited lumen **(Fig. 2E).** Normal cell borders, normal nuclei, and considerable pseudostratefication were seen in the excretory duct **(Fig. 2F).**

4- **Cholesterol rich diet+Cinnamon+ Ginger:** Microscopic investigation of this group demonstrated that the gland's usual structural characteristics were mostly intact. This was demonstrated by the retention of characteristic acinar morphology and recognizable normal secretory cell organization in spherical shaped acini. The parenchyma of the gland revealed serous acini with pyramidal cells and a basally positioned nucleus. The cellular boundaries were also addressed. Acinar cell cytoplasm seemed basophilic. The intercalated duct has a small lumen with cuboidal cells and a usually visible nucleus. Striated ducts exhibited cellular boundary renewal. Some nuclei were seen to be hyperchromatic (Fig. 2G). The excretory duct had a large lumen and conspicuous renewal of pseudostratefication with goblet cells in-between the stratified cells. The nucleus of duct cells was heavily stained**.**

5- □- *Immunohistochemical* Results:

A- Anti-Vascular Endothelial Growth Factor (VEGF) Immunological Results:

1- Control Group: secretory cells of serous acini and epithelial lining cells in the intercalated and striated ducts showed strong to moderate cytoplasmic immunoreaction for (VEGF) **(Fig. 3A).**

2- Cholesterol Rich Diet Group: immunoreaction to (VEGF) revealed that secretory cells of serous acini and epithelial lining cells in the intercalated and striated ducts showed negative to week cytoplasmic immunoreaction for (VEGF) **(Fig. 3B).**

3- Cholesterol Rich Diet+ Atorvastatin Group: The immunoreaction patterns of (VEGF) in the submandibular gland of rats fed a high fat diet for three months and treated with Atorvastatin tablets for one month demonstrated that secretory cells of serous acini had a moderate immunoreaction in terms of qualitative color intensity immune reaction. Peripheral acinar cells revealed moderate (VEGF) staining, indicating the presence of myoepithelial cells in the intercalated and striated ducts, which showed moderate cytoplasmic immunoreactivity for (VEGF) **(Fig. 3C).**

4- **Cholesterol Rich Diet+ Cinnamon+ Ginger Group:** VEGF immunoreactivity patterns in the submandibular gland of rats fed a high fat diet for three months and treated with Cinnamon powder+ Ginger powder for one month exhibited a strong to moderate response in the cytoplasm of the secretory cells of the serous acini. Peripheral acinar cells had a robust immunological response, revealing myoepithelial cell expression. Intercalated and striated cells exhibited cytoplasmic immunological responses ranging from high to mild. Basement membranes of duct cells reacted strongly to moderately **(Fig. 3D).**

Discussion

Cholesterol is crucial for the structural integrity of cell membranes and serves as a precursor for steroid hormones and bile acids. Obesity and a high saturated fat diet are two of the most common causes of hypercholesterolemia **(Deepak et al., 2008).**

Lowering cholesterol levels can be accomplished by lifestyle modifications as well as the use of pharmaceutical therapies such as statins, bile acid sequestrants, nicotinic acid, and cholesterol absorption inhibitors **(Stone et al., 2014).**

The use of biologically produced dietary supplements in health promotion is fast growing. Dietary supplements have been proven to be a safe and effective alternative method for the prevention and/or treatment of dyslipidemia and concomitant cardiovascular events, with little side effects and toxicity **(Gonzalez et al., 2010).**

So, the present study was designed to compare the effect of atorvastatin, ginger, and cinnamon on the submandibular salivary gland of hypercholesterolemic albino rats.

According to prior studies, hypercholesterolemia was created in albino rats by exposing them to a fat-rich diet for an extended length of time (4 months), which leads in obesity in the experimental animals. One of the key causes for lipid accumulation in salivary glands is feeding rats a high fat diet with cholesterol crystals. **(Zalar et al., 2021).** As lipid intake is greater than usage during first several days, excess lipids is preserved in secretory cell cytoplasm of salivary glands as droplets **(Nagato and Masuno, 1993).**

In the cholesterol-rich diet group, hypercholesterolemia was induced by feeding albino rats a high-fat diet laced with cholesterol crystals, resulting in a significant increase in cholesterol levels, which agrees with previous findings reported by **Khosla and Sundram (1996),** who used albino rats fed different amounts and types of fats and found an increase in plasma lipid profile.

Many studies have found that nutrition has a significant impact on the development of hyperlipidemia and atherosclerosis. Several animal and human investigations have concluded that cholesterol and saturated fatty acids promote hypercholesterolemia by increasing total cholesterol and altering the lipoprotein pattern. Cholesterol feeding has frequently been used to elevate cholesterol levels in order to cause hypercholesterolemia and associated metabolic abnormalities in numerous animal models **(Arnett et al., 2019).**

The current investigation found that supplementing a high cholesterol diet was enough to cause hyperlipidemia. **Arafa (2005), Dhulasavant et al. (2010), and Iqbal et al. (2015)** all reported similar findings, concluding that providing a high cholesterol meal elevates blood lipid profile markers.

A lipid profile for rats fed a high fat diet was investigated in the current study, which revealed a significant increase in plasma cholesterol and low-density lipoprotein level (LDL) while there was a significant decrease in high density lipoprotein (HDL). These findings agreed with previous findings that stated that hyperlipidemic diet increased serum triglyceride, cholesterol, total lipid, and low-density lipoprotein (LDL) and decreased high density lipoprotein (HDL) **(Pisiriciler et al., 2008).**

Furthermore, **Ioanna and Christina (2010)** discovered that a hyperlipidemic diet resulted in a considerable rise in total cholesterol, LDL with a negligible increase in rats' weight, and a significant drop in HDL, corroborating our statistical findings.

Furthermore, dietary fat and cholesterol have been found to influence lipoprotein responsiveness and apolipoprotein gene expression, which in turn alter plasma cholesterol concentrations **(Nicolosi, 1997).**

Histological examination of submandibular salivary gland of the albino rats who fed high fat diet for 4 months showed that high-fat diet altered the histological structure of the submandibular salivary gland. It caused loss of the normal morphological pattern of acinar cells.

Redman (2008) and Pişiriciler (2008) discovered that a high fat diet causes massive changes in the parotid salivary gland, and that the accumulation of lipids in the salivary gland's parenchymal cells causes multiple inflammatory changes that may restrict the diffusion of nutrients and oxygen, negatively affecting the function and survival of the parenchymal cells. Furthermore, intracellular lipids generate a large number of intracellular vacuoles. These vacuoles might be linked to degenerative alterations inside secretory cells, most of which are fatty in nature (fatty degeneration), which would explain the current findings..

These findings supported prior observations that a high-fat diet increased lipid buildup in secretory cells. High fat consumption causes significant intracellular lipid buildup in the salivary glands. This lipid intake exceeded utilization, resulting in the buildup of surplus lipids in the salivary gland cells as droplets. These lipid droplets put pressure on the acini borders, causing them to seem degraded and distorted **(jiang et al., 2005).**

Submandibular salivary glands from rats on a high fat diet reveal substantial abnormalities in the duct system, with intercalated ducts exhibiting aberrant architecture and ill-defined cell borders. Striated duct cells occurred in the absence of basal striations. The cytoplasm seemed degraded, and the majority of the nuclei showed symptoms of necrosis. The excretory channel has lost its pseudo stratification. The regular architectural pattern was lost in the granular convoluted tubules.

These findings corroborated **Moubarak's (2008)** claim that the buildup of lipid droplets in between secretory parts exerts pressure on their edges, causing them to seem distorted. The abnormal deteriorated characteristics of the secretory ducts were also explained, as the ducts seemed degenerated and dilated due to salivary secretion buildup and exocytosis failure.

Starkov and Wallace (2002) explained dilated striated ducts and stagnant secretion, claiming that dilatation and stagnant secretion in the lumen of some ducts could be presumably due to mitochondrial damage, which could lead to ATP depletion and subsequent failure of biosynthesis and membrane pumps. As a result, the cells had insufficient energy to transfer secretions, resulting in ductal dilatation and obstruction.

This group has dilated blood arteries with extravasated red blood cells. These findings were consistent with prior studies that demonstrated cellular infiltration and dilated blood arteries congested with red blood cells in rats fed a high-fat diet. These discoveries might be part of an inflammatory response to bring about more

Previous research has linked a high-fat diet to atherosclerosis and hypertension. As a result, frail atherosclerotic arteries were easily ruptured within glands, explaining the current findings **(Selim, 2013).**

In the current investigation, albino rats fed a high fat diet for four months were given 10mg/kg BW Atorvastatin pills for one month as one of the statin medicines. Atorvastatin was chosen since it is one of the most commonly used therapeutic lipid-lowering medicines **(Lie et al., 2003).**

Hisao et al., (2014) discovered that utilizing Atorvastatin at 10mg/kg BW in hyperlipidemic rats resulted in a substantial drop in total cholesterol levels and a reduction in LDL, which explains our pharmacological dose decision.

Biochemical results of this group showed significant decrease in total cholesterol level, LDL and significant increase in HDL compared with cholesterol group.

These findings were consistent with previous findings reported **by Sehayek et al., (1994),** who stated that statin inhibition of HMG-CoA reductase causes a decrease in intracellular cholesterol by activating a protease that slices the sterol regulatory element binding proteins (SREBPs) from the endoplasmic reticulum. SREBPs are translocated to the nucleus, where they boost LDL receptor gene expression. The decrease in cholesterol in hepatocytes causes an increase in hepatic LDL receptors, which dictates the decrease in circulating LDL.

Stein et al., (1998) said that all statins lower LDL cholesterol non-linearly, dose-dependently, and efficacy on triglyceride reduction tracks LDL cholesterol reduction after administration of a single daily dosage.

Furthermore, several investigations have demonstrated that statins reduce LDL via blocking hepatic production of apolipoprotein B-100, the LDL receptors. This may explain why Atorvastatin can lower LDL in hypercholesterolemic individuals when LDL receptors are not functioning **(Raal et al., 1997).**

The considerable rise in HDL was consistent with recent findings that Atorvastatin lowers plasma cholesterol in mice via lowering vascular low-density lipoprotein (VLDL) synthesis. The rise in HDL was associated by a decrease in hepatic CETP mRNA expression, as well as a drop in plasma CE transfer activity. The fact that mice do not normally produce CETP appears to limit the Atorvastatin-induced rise in HDL-cholesterol in mice **(Willeke et al., 2007).**

Laufs et al. (1998) explained the return of typical acinar appearance with its histological characteristics in this group, reporting that endothelial dysfunction constitutes an early event in the development of atherosclerotic lesion, which is triggered by hypercholesterolemia. Hypercholesterolemia lowers endothelial cells' ability to create nitrous oxide (NO), which modulates the endothelial's anti-atherosclerotic activity. Statins significantly improve endothelial function by lowering cholesterol.

Wagner et al., (2000) reported previous results that statins block the generation of O2- by endothelial cells, causing changes in the NO-/ O2- balance, which resulted in the restoration of endothelial cell function.

These findings agreed with previous findings that statins improve vasomotor regulation of blood flow, and that Atorvastatin's modification of lipid profile leads to an increase in endothelium dependent vasodilation, which leads to an increase in blood flow to the damaged area, which leads to its repair. Statin treatment resulted in the creation of new blood vessels **(Pan et al., 2021).**

Bellosta et al., (2000) explained that statins can influence G proteins by blocking their prenylation and thereby lowering the inflammatory response in hypercholesterolemic rats.

A histological study of the same group indicated that the granular convoluted tubules were dilated. Some of the granular convoluted tubules had cytoplasmic vacuolar degeneration, with total loss of intercellular boundaries. Other granular tubules have relatively normal cell borders and nuclei. Several studies have indicated that treating hypercholesterolemia with statins results in a decrease in both cholesterol and coenzyme Q10 (Co Q10) production **(Berthold et al., 2006).**

CoQ10 (Ubiquinone) is a water-insoluble component of nearly all cell membranes. It is an important part of the mitochondrial electron transport system **(Littarru and Langsjoen, 2007).**

Kumar et al. (2007) demonstrated that treatment of hyperlipidemic rats with Atorvastatin caused various degrees of pancreatic acinar degeneration, including the loss of normal architecture and empty spaces among the pancreatic acini. Acinar cells have poorly defined cell boundaries. This explains the degraded effect observed in our histology data.

Previous research has shown that any severe illness or toxic condition that affects the pancreas can also impact the salivary gland acini and ducts, making salivary glands parallel with pancreatic disease diagnosis because it is the first organ affected by pancreatitis **(Tiffon, 2020).**

Yassien and El-ghazouly (2020) asserted that atorvastatin has harmful effects on the pancreas of hyperlipidemic individuals, adding to the prior explanation.

The existence of cytoplasmic vacuoles in convoluted tubules in the current experiment may be due to intracellular calcium rise, which caused disruption and elevation of exocytosis. Some writers cited autophagocytosis as a cause of vacuolations. Furthermore, the authors said that acinar cell vacuolization is regarded a degenerative hint of pancreatitis, which agreed with our findings **(Abd El-Rahman et al., 2011).**

The current study The effects of ginger and cinnamon on hypercholesterolemia were compared to the synthetic medication Atorvastatin. Medicinal plant use has effectiveness, tolerability, adequacy, and no toxicity **(Amalraj and Gopi, 2017).**

Previous research on ginger as a hypolipidemic herbal medication led to its use as a herbal medicine. It was said that employing medicinal herbs from several families, one of which being ginger (Zingiber officinale), plants were screened for anti-lipase activity, and the study discovered that Zingiber officinale did not exhibit any lipase inhibitor effect. This suggests that ginger was able to lower lipid profile without affecting pancreatic lipase levels, reducing its pancreatic side effects **(Han et al., 2001).**

It is well known that both dried and fresh ginger are considered medicinal products in some countries; however, the dehydration process preserves the physical and chemical properties of ginger active compounds, which is consistent with the current study in which ginger powder was used and added to distilled water daily for one month **(Dnur and Goyal, 2005).** Ginger powder was chosen based on earlier research that found ginger to be a safe herbal medication when administered at a dosage of 25-100 mg/kg **(Haksar et al., 2006).**

In this study biochemical results showed a significant decrease in cholesterol and LDL level and significant increase in HDL level when evaluated by blood lipid profile comparing with cholesterol group.

These findings were consistent with previous findings by **El Rokh et al., (2010),** who reported that giving ginger to hypercholesterolemic albino rats for 2 and 4 weeks resulted in a significant decrease in all lipid profile parameters, and added that ginger is a powerful herb affect via inhibition of total cholesterol, LDL-C, and triglyceride increases, and the decrease of HDL-C by down-regulating lipid accumulation and up-regulating adiponectin expression in

Fuhrman et al. (2000) discovered that consuming ginger reduces the development of atherosclerosis by lowering plasma LDL and cholesterol levels in apolipoprotein E-deficient mice. This study also found that consuming ginger extract lowers cellular absorption of oxidized LDL, probably due to steric alteration of plasma lipoprotein receptors.

Furthermore, **Hojjat et al. (2015)** compared the effect of some statin drugs to ginger administration and discovered that ginger caused a significant increase in high density lipoproteins due to niacin (a constituent of ginger), which causes a reduction in the catabolic rate of HDL.

Previous research supports the current results that ginger's tissue protecting efficacies can be explained by lowering the circulating lactate dehydrogenase enzyme (LDH). LDH is an enzyme that is found in nearly every cell of your body, including the blood, muscles, brain, kidneys, and pancreas. Sugar is converted into energy by the enzyme. In addition, ginger reduces aspartate aminotransferase AST levels in rats under oxidative stress circumstances. AST is an enzyme located mostly in the liver. When AST-containing cells are destroyed, the AST is released into the bloodstream, which explains the reparative action of ginger and our findings **(Helal et al., 2012).**

In addition to the benefits listed above, ginger powder decreases the degree of lipid peroxidation and increases plasma antioxidant capacity. Plasma-free radicals are reduced when plasma antioxidant capability is increased **(Afshari et al. 2007).**

Furthermore, these findings were consistent with prior study, which discovered that treating hyperlipidemic rats with ginger resulted in a strong hypolipidemic impact of ginger and indicated that its hypolipidemic activity is related to that. The [E]-8b, 17-epoxylabd-12-ene-15,16-dial (ZT) compound isolated from ginger reduced plasma cholesterol levels in rats with experimentally induced hypercholesterolemia by inhibiting cholesterol biosynthesis, and it also interfered with cholesterol biosynthesis in mouse and rat homogenate liver **(Tanabe et al. 1993).**

Edema develops when an abnormally large amount of fluid collects in the tissues, either within cells (cellular edema) or within the collagen mucopolysaccharide matrix that is spread in

the interstitial spaces (interstitial edema). In the case of congestion, interstitial edema may develop from an abnormal increase in the hydrostatic pressure pressing across the microvascular walls **(Scallan et al., 2010).**

In a prior study using a carrageenan-induced rat paw edema model, ginger extract alleviated carrageenan-induced edema in rat paws. Ginger's impact was dose-dependent, with ginger dosages of 100 and 200 mg/kg decreasing paw edema by a percentage. which discussed the usage of ginger and its effect on acinar cells **(Zakaria et al., 2010).**

The presence of cytoplasmic vesicles and vacuoles, as well as hyperchromatic nuclei in certain duct cells. These findings could be explained by the fact that the ginger dose was insufficient to repair the damage done to the cells by the high fat diet. Previous research found that when comparing several doses of ginger powder with rats fed a high fat diet, 200 mg/kg body weight was the most suitable safe dose of ginger that affected low density lipoproteins stored in cells **(Venkata et al., 2017).**

The improved results in this study could also be attributed to the pharmacological action of ginger, which increases the activity of hepatic cholesterol 7a-hydroxylase, a rate-limiting enzyme in the biosynthesis of bile acids, and stimulates the conversion of cholesterol to bile acids, resulting in cholesterol excretion from the body **(Srinivasan and Sambaiah 1991).**

These findings agreed with those of **Amer et al. (2013),** who found that 100 mg of ginger taken orally once a day reduced the histopathological effects on liver and spleen tissues.

Ginger's antioxidant activity seems to be an underlying possible mechanism increasing ginger's hepatoprotective impact. Ginger's antioxidant action may prevent membrane lipid peroxidation, which causes cell damage and necrosis **(Abdel-Azeem et al., 2013).**

The use of 6 mg cinnamon powder corresponds with the findings of **Khan et al. (2003),** who determined that the bark of cinnamon at various dosages controls total cholesterol and triglyceride levels as well as free fatty acid levels in type 2 diabetic individuals due to its significant lipolytic action. As a result, it suggests that cinnamon powder is effective in reducing hyperlipidemia-related lipid profile elevations.

It was stated that most drugs used to treat hypercholesterolemia do not reduce triglyceride concentrations, but cinnamon powder equivalent to 6 gm/kg body weight reduced it by 41.81% at treatment day 60 in the current study, and this is important in preventing cardiovascular diseases **(Zahid et al., 2016).**

Furthermore, **Khan et al. (2003)** shown that cinnamon has a direct impact in lipid metabolism, where cinnamon protects hypercholesterolemia and hypertriglyceridemia and decreases free fatty acid and TG levels through its significant lipolytic action.

Other researchers discovered that cinnamon activates PPAR gamma and alpha, resulting in better insulin resistance and lowered fasting LDL in high caloric diet-induced obesity mice, therefore regulating obesity-related diabetes and hyperlipidemia **(Sheng et al., 2008).**

These findings were consistent with **Steiner's (2003)** explanation that regeneration of hepatocytes affected by hyperlipidemia was accomplished by treating hyperlipidemic rats with

cinnamon powder because cinnamon contributes to cholesterol depletion in hepatocytes and increases clearance of low-density lipoproteins (LDL) from the blood by upregulating hepatic LDL receptors and reducing LDL entry into circulation.

These findings are consistent with those of **Zari and Allogmani (2009),** who found that cinnamon supplementation resulted in a significant decrease in total cholesterol, triglycerides, and LDL, as well as a significant increase in HDL concentration in streptozotocin-induced diabetic rats. As a result, cinnamon powder may be effective in modulating the metabolism of specific lipoproteins, which leads in

These findings were consistent with prior studies in which hyperlipidemic mice treated with cinnamon for four weeks exhibited histological increase in liver hepatocyte cells. Histological investigation of rat liver sections revealed less obvious histopathological alterations, including a few scattered hepatocytes with minute vacuoles or pyknotic nuclei **(Arisha et al., 2020).**

Niknezhad et al. (2019) investigated the regenerative and repairing properties of cinnamon and concluded that these reparative effects were attributable to cinnamon's antioxidant activity, which caused either suppression or avoidance of free radical formation. They also said that cinnamon reduced necrosis, inflammatory cell infiltration, and liver fibrosis, and ascribed this to its capacity to rebalance antioxidant enzymes to erase cellular damage.

Previous research also explained that the relief of histopathological alterations in the liver of obese rats observed after cinnamon treatment was due to its eugenol, polyphenols, and flavonoids, which reduced the level of oxidative stress, inflammatory, and apoptotic biomarkers and induced an anti-obesity effect in rats fed on HFD **(Abd El-Rahman, 2018).**

Similarly, **El Ebiary and Khalaf (2015)** investigated the effect of high fat diet and the protective role of cinnamon when rats were fed a high fat diet for 60 days and discovered that cinnamon administration in conjunction with HFD ameliorated the hazardous effect of HFD on the structure of the liver of experimental rats, which they attributed to cinnamon's antioxidant, anti-inflammatory, and lipolytic activity.

Another explanation is that cinnamon may inhibit hyperlipidemia by decreasing hepatic 5-hydroxy-3-methylglutaryl-co-enzyme A (HMG-CoA) reductase activity (a rate-limiting enzyme involved in regulating cholesterol metabolism or biosynthesis and decreasing serum TC level); thus, it acts as a hypocholesterolemic agent **(Abd El-Rahman, 2018).**

These findings reflect cinnamon's ability to repair the damage caused by a high fat diet and are consistent with previous findings that cinnamon's lipolytic role in lowering hypercholesterolemia is attributed to its ability to decrease the expression of proteins responsible for the induction of lipogenesis **(Tuzcu et al., 2017).**

Cinnamon has an enhancing effect because it contains quercetin (flavonoid), which has been shown to be effective in lowering hyperlipidemia, preventing oxidative injury and cell death, and reducing de novo synthesis of fatty acids, as well as cholesterol biosynthesis and lipoprotein formation **(Ahmadi and Shahri, 2019).**

Niknezhad et al. (2019) discovered that cinnamon suppresses necrosis, inflammatory cell infiltration, and liver fibrosis, and ascribed this to its capacity to rebalance antioxidant enzymes to eradicate cellular damage. Because cinnamon contains eugenol, polyphenols, and flavonoids, which lower oxidative stress, it alleviated the histological abnormalities in the liver of obese rats.

This group's blood cholesterol, high density lipoprotein, and high-density lipoprotein levels were evaluated, and there was a substantial drop in cholesterol and low-density lipoprotein compared to the cholesterol group. The current statistical findings showed a significant increase in high density lipoproteins, which is consistent with previous findings that showed that combining ginger and cinnamon effectively reduced cholesterol plus LDL cholesterol content in hyperlipidemic rats **(Salah and Moustafa, 2016).**

Mahmoud et al., (2022) demonstrated that adding cinnamon combined with ginger to the diet of hyperlipidemic rats in multiple concentrations resulted in a significant decrease in total triglycerides, cholesterol, low-density lipoproteins, and a significant increase in high density lipoproteins, resulting in less lipid accumulation in liver cells and less histopathological changes in liver cells..

Previous research found that consuming half a teaspoon of cinnamon daily can reduce low density lipoprotein and cholesterol levels in blood tests in rats fed a high fat diet for four months **(Khan et al., 2003).**

Simultaneous administration of ginger resulted in a significant decrease in serum total cholesterol, LDL-cholesterol, triglycerides, and a significant increase in HDL-cholesterol, indicating a beneficial modulatory influence on cholesterol metabolism and turnover **(Heeba et al., 2010).**

Ginger's plasma lipid-lowering impact might be due to a variety of mechanisms, including interruption of cholesterol absorption from the GI tract and interference with cholesterol production in the liver **(Newall et al., 1996) (Fuhrman et al., 2000).**

Several lines of evidence suggest that ginger includes antioxidants with hypocholesterolemic and anti-atherogenic characteristics, which may be ascribed to the prevention of LDL oxidation and the reduction of HMG-CoA reductase activity **(Stoilova et al., 2007).**

Anti-vascular endothelial growth factor VEGF immunohistochemistry investigation of albino rats' hypercholesterolemic submandibular salivary gland revealed a negative to week immune reactivity to VEGF in acini and duct cells of the submandibular salivary gland.

These findings were consistent with previous research, which found that a negative to week reaction to vascular endothelial growth factor (VEGF) in hypercholesterolemic patients was due to decreased migratory responses to VEGF, most likely due to internalization and degradation of the VEGF receptor VEGFR2 and decreased VEGF downstream signaling pathways such as PI3K/PKB and ERK1/2 **(Jin et al., 2013).**

Previous research has found that individuals with hypercholesterolemia had reduced micro vascular proliferation than patients with normocholesterolemia, and the expression of

VEGF decreases with hypercholesterolemia. Other experimental findings reinforce the idea that disturbed lipid metabolism might hinder angiogenesis **(Murugesan and Fox, 1996).**

Another discovery established that oxidized LDL decreases endothelial cell motility. **Chen et al. (1997)** demonstrated that hyperlipidemic angiogenesis impairment is connected with decreased availability of basic fibroblast growth factor (bFGF). They discovered that when vascular endothelial cells from different species (human, rabbit, and bovine) are deprived of bFGF, they are unable to reproduce or form micro capillaries.

In favor of this notion, the current investigation established an inverse association between hypercholesterolemia and endothelial cell growth factor expression (bFGF and VEGF). Furthermore, individuals with reduced endothelial basic fibroblast growth factor (EbFGF) and VEGF expression had decreased coronary microvascular disease (MVD) **(Murugesan and Fox, 1996).**

Duan et al. (2000) observed that rats with dietary hypercholesterolemia had lower ischemia-induced angiogenesis as well as hypercholesterolemia-related angiogenesis impairment.

Statins are a class of medications that limit cholesterol manufacture and have a lipid-lowering effect; this also explains other indications such as inflammation and cancer treatment **(Faggioto and Paoletti, 2003).**

Rats treated with Atorvastatin had moderate positive immunoreactions to VEGF in acinar and duct cells. This is consistent with **David (2011),** who investigated the effect of Atorvastatin on the pancreas of adult male albino rats and discovered that pancreatic cells treated with Atorvastatin had a robust immunological response to VEGF.

Sadek and Khattab (2017) have said that VEGF is an essential angiogenesis mediator. As a result, VEGF may be elevated as a compensatory strategy for pancreatitis, with eventual pancreatic regeneration; directly through activation of the maturation of progenitor ductal epithelial cells and indirectly through augmentation of capillary neoformation**.**

The current findings are also consistent with a prior work that evaluated VEGF and Matrix Metalloproteinase-9 in the periodontium of rats treated with atorvastatin and found significant immunoreactivity **(Umut et al., 2014).**

The present immunological findings in hypercholesterolemic rats treated with Ginger revealed a positive moderate immune response to vascular endothelial growth factor (VEGF). These findings were consistent with those of **Nakanishi et al. (2007),** who investigated the expression and synthesis of vascular endothelial growth factor in oral mucosa analogues and ascribed positive VEGF expression in epithelium to an increase in epithelial differentiation following tissue healing.

Another demonstration said that VEGF is a necessary pro-angiogenic growth factor that can maintain the angiogenic balance during active tissue inflammation and ulcer healing. Ginger extract increased the expression of both bFGF and VEGF **(Joshua and Catherine, 2010).**

Ruiz et al. (2010) demonstrated that VEGF expression reflected a low degree of inflammation following decreased antigenic stimulation. Furthermore, the scientists found a link between VEGF immunoexpression and microvascular density and the strength of inflammatory infiltrates.

Intercalated, striated, and excretory ducts had cytoplasmic immune responses ranging from strong to mild. Basement membranes of duct cells reacted strongly to moderately. These findings corroborated prior research that found VEGF in duct epithelial cells and certain myoepithelial cells in normal salivary glands. Flk-1 and Flt-1, two VEGF receptors, immunolocalized very identically to VEGF **(Taichman et al., 1998).**

Strong immunization in duct cells in this group also eliminated the possibility that one of VEGF's activities is the creation and maintenance of ductal structures. In prostatic and mammary tumors, a similar trend in tubule development has already been documented **(Taichman et al., 1998).**

Previous evidence demonstrated that salivary gland cells are capable of producing and secreting VEGF under normal conditions, which explains the intense immune response in this group, as ginger aids in the repair of diseased submandibular salivary gland cells and may restore them to normal **(Nishimura et al., 2002).**

Anti-VEGF immune response in hypercholesterolemic rats treated with cinnamon+ginger demonstrated a robust to moderate immunoreaction in acinar cells and ducts.

These findings were consistent with a prior study that used cinnamon-treated rats and found VEGF expression in lung tissue. The intense favorable reaction was discovered in that investigation, and cinnamon therapy restored the damaging effect and enhanced VEGF expression. There was, however, no statistically significant change in VEGF expression between the cinnamon-treated and control groups. These findings show that cinnamon may have a role in VEGF expression **(Turul and Gökçen, 2022).**

Abdel-Kawi et al., (2022) investigated the effects of cinnamon on ethanol-induced stomach ulcers in rats. Cinnamon significantly enhanced the amount of TNF- and PGE content when tested utilizing a VEGF immune response. Furthermore, cinnamon therapy raised VEGF immunoreactivity substantially.

Furthermore, cinnamon and its active component have a new angiogenic factor activity. Cinnamon promotes angiogenesis, with cinnamon's potential to induce novo vessel development equivalent to that of the well-established angiogenic factor VEGF. Vascular endothelial growth factor (VEGF) is an endothelial cell-specific growth factor and the primary regulator of angiogenesis **(Ferrara et al., 2003).**

Previous research found that cinnamon stimulated human umbilical vein endothelial cells (HUVEC), resulting in increased cell proliferation, chemotactic motility, and a robust induction of tube network development. This study also revealed that the mechanism by which cinnamon induces angiogenesis is similar to that of VEGF, which needs VEGF production for angiogenic action **(Ko et al., 2009).**

The positive immunological response in this group is also explained by some who claim that cinnamon increases Flk-1/KDR expression, which is a molecular target of vascular endothelial growth factor (VEGF). Cinnamon enhances active VEGF binding to the receptor Flk-1/KDR, which mediates the VEGF-dependent mitogenic action **(Ko et al., 2009).**

According to **Abdel-Azeem et al. (2013),** the lowering of liver enzymes with cinnamon and ginger extract might be attributed to the antioxidant action of cinnamic in cinnamon and zingerone, catechin in ginger extract. Cinnamon supplementation significantly decreased the ALT enzyme activity in butter-fed mice.

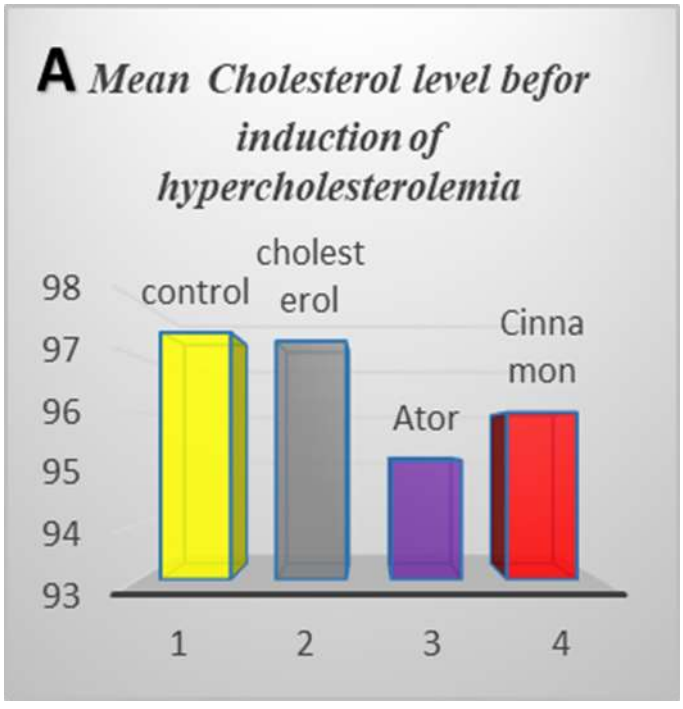
Hassanen (2010) discovered that rats treated with ginger and cinnamon had less aberrant liver histology.

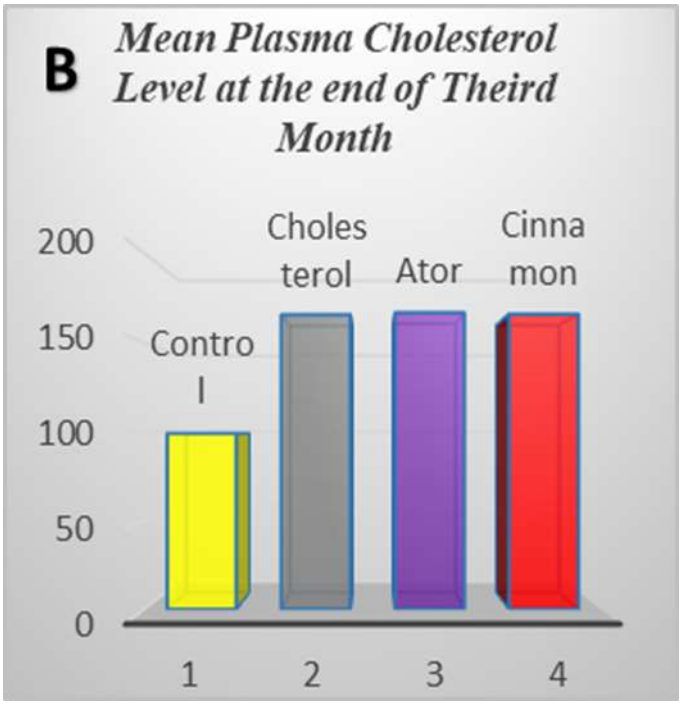
According to **Salah and Moustafa (2016),** hyperlipidemic rats given 1% and 2% of their diet with combined Ginger and Cinnamon extracts showed the greatest protective impact on liver cells and function as anti-obesity medications.

Mahmoud et al., (2022) discovered that rats given a combination of 100 mg ginger and 100mg cinnamon showed no histological alterations in liver cells.

Another study, **Mousa et al., (2021),** found that ginger treatment resulted in a beneficial alteration in liver histological characteristics..

Conclusion: To varying degrees, hypercholesterolemia has a negative impact on the anatomy of the parotid gland. The use of Atorvastatin as a synthetic line of treatment for hypercholesterolemia improved submandibular gland tissue and blood cholesterol levels. Cinnamon+ Ginger powder administration improved submandibular gland tissue as a natural herbal remedy for high cholesterol levels in the blood.





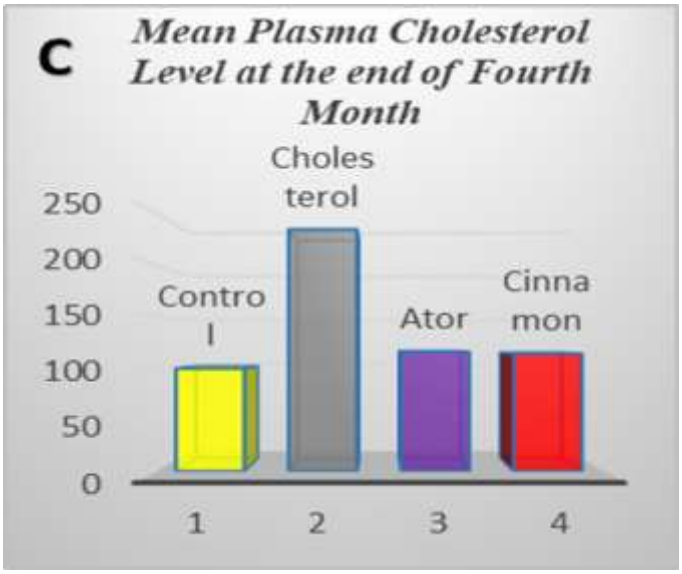
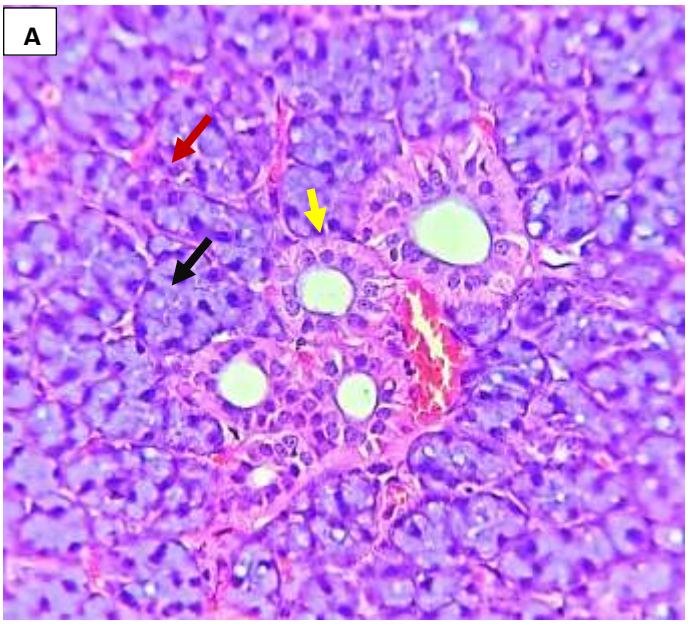
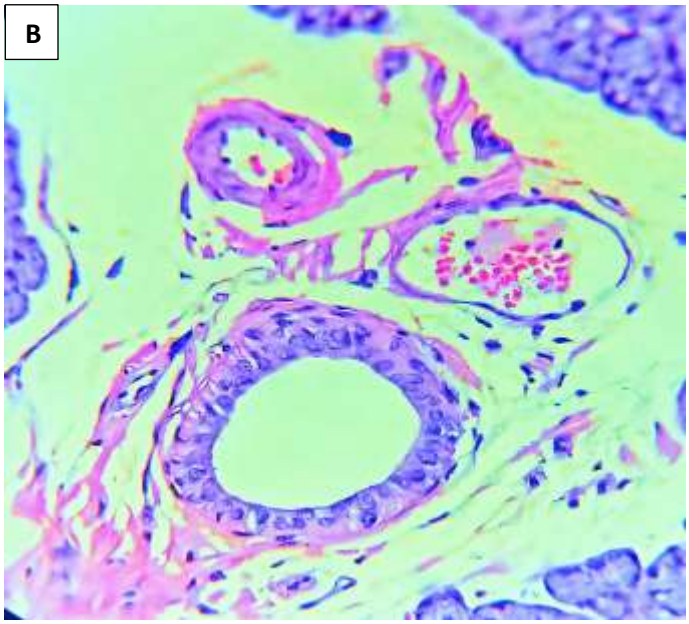
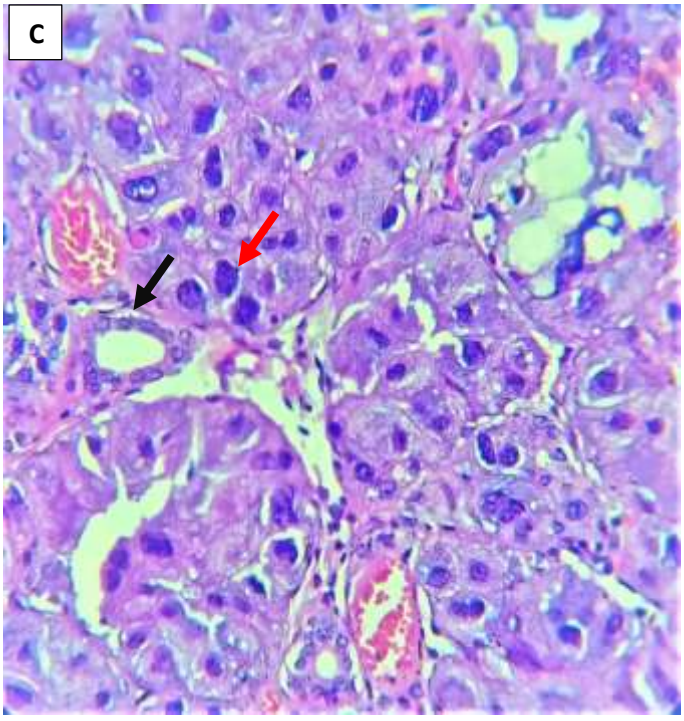


Fig:1: (A): Bar chart showing the mean plasma of cholesterol level before induction of hypercholesterolemia, **(B):** Bar chart showing the mean plasma of cholesterol level after induction of hypercholesterolemia, **(C):** Bar chart showing the mean cholesterol level at the end of the fourth month of all groups.



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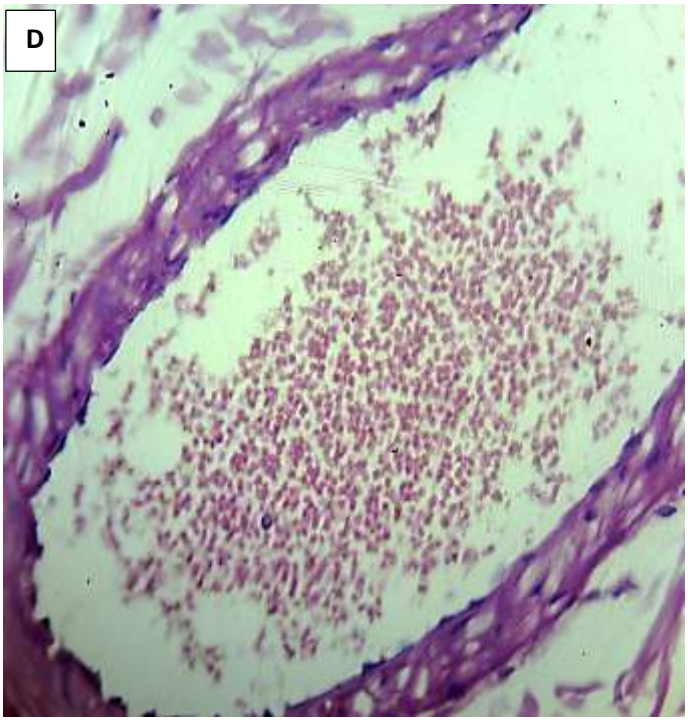
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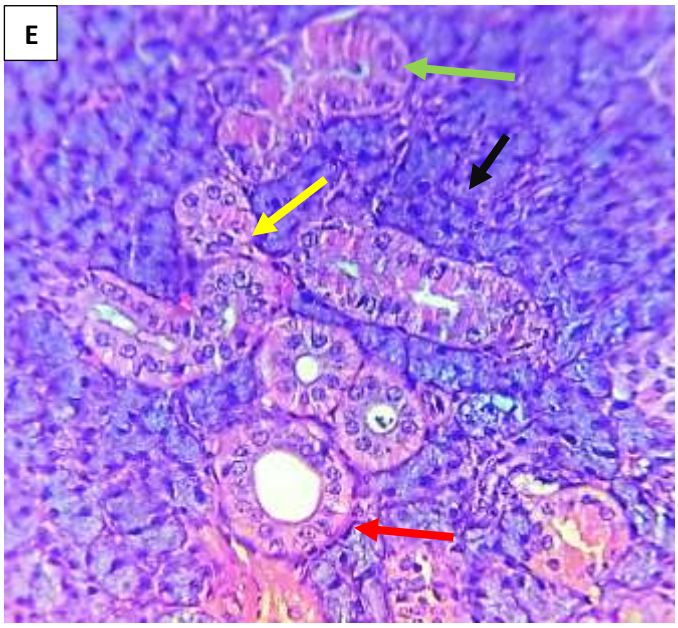
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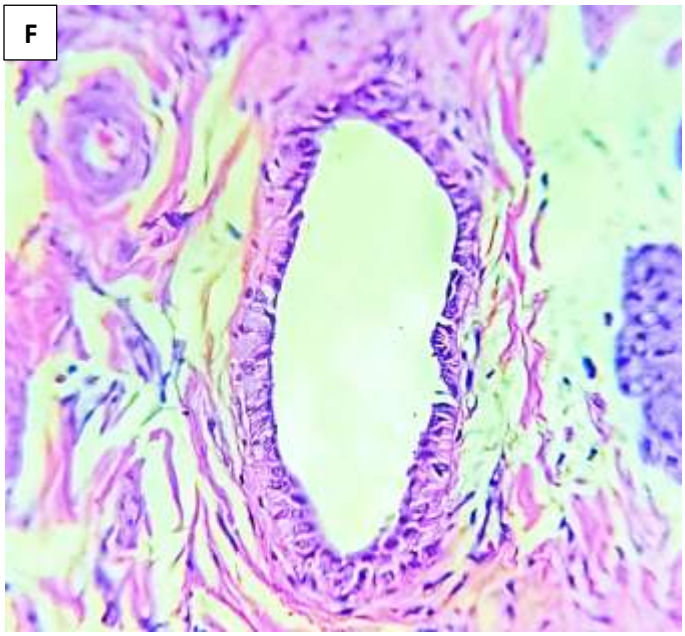
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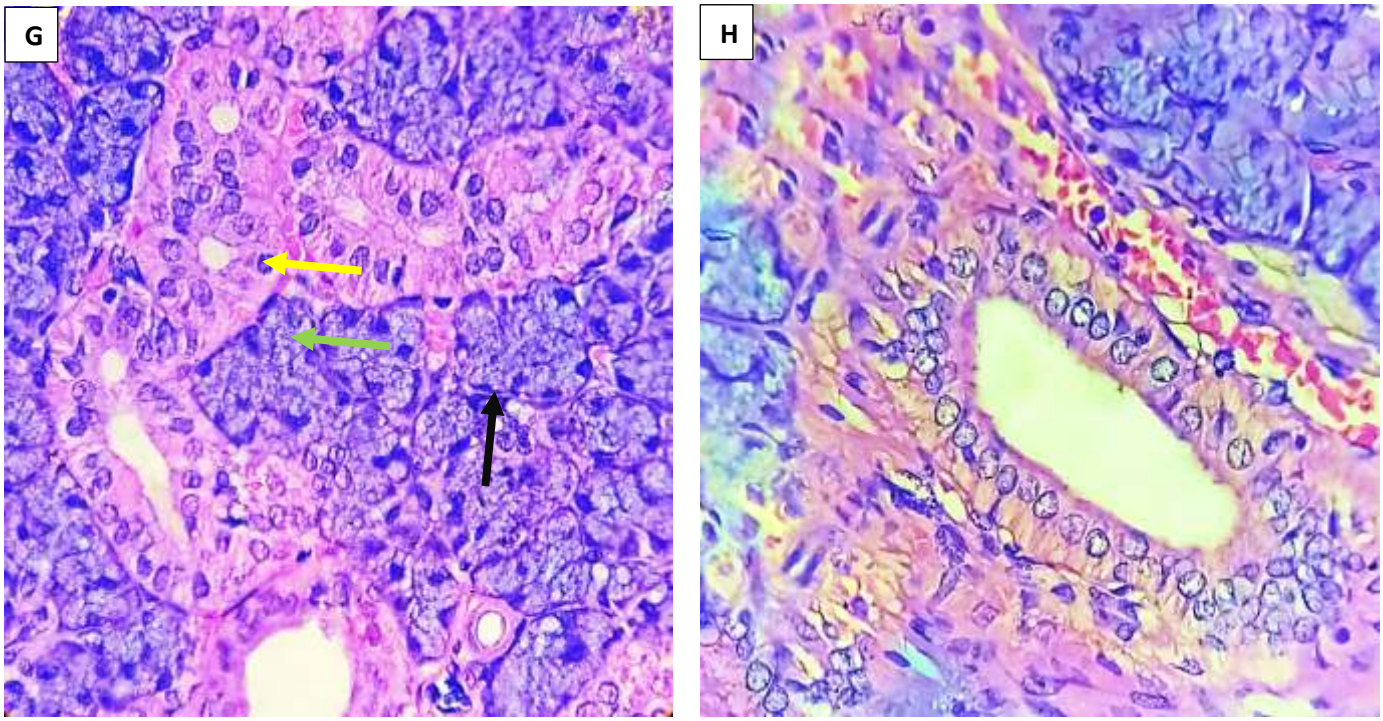

Fig. 2: (A) A photomicrograph of the control group showing serous acini (black arrow). Intercalated duct (red arrow), striated ducts (yellow arrow), **(B):** A photomicrograph of control group showing excretory duct with marked pseudostratefication **(C):** A photomicrograph of cholesterol group showing serous acini with vacuolated cytoplasm and abnormal nuclear mitosis with hyperchromatic nucleus (red arrows), striated ducts with loss of basal striation (black arrows), dilated blood vessel congested with RBCs (green arrow), **(D):** A photomicrograph of cholesterol group showing excretory duct with loss of pseudostratefication and red blood cells congestion. **(E):** A photomicrograph of atorvastatin treated group showing serous acini with cytoplasmic vacuoles (black arrows), intercalated duct (yellow arrow), striated ducts with basal striations (red arrows), granular convoluted tubule with marked cytoplasmic granules and narrow lumen (green arrow). **(F):** A photomicrograph of the same group showing excretory duct with marked pseudostratefication. **(G):** A photomicrograph Cinnamon+ Ginger treated group showing normal spherical acini (green arrow). Intercalated duct (black arrow) and striated duct with basal striations (yellow arrows). **(H):** A photomicrograph Cinnamon+ Ginger treated group showing Excretory duct with marked pseudostratefication and clear lumen **(H & E, x 400, 640).**

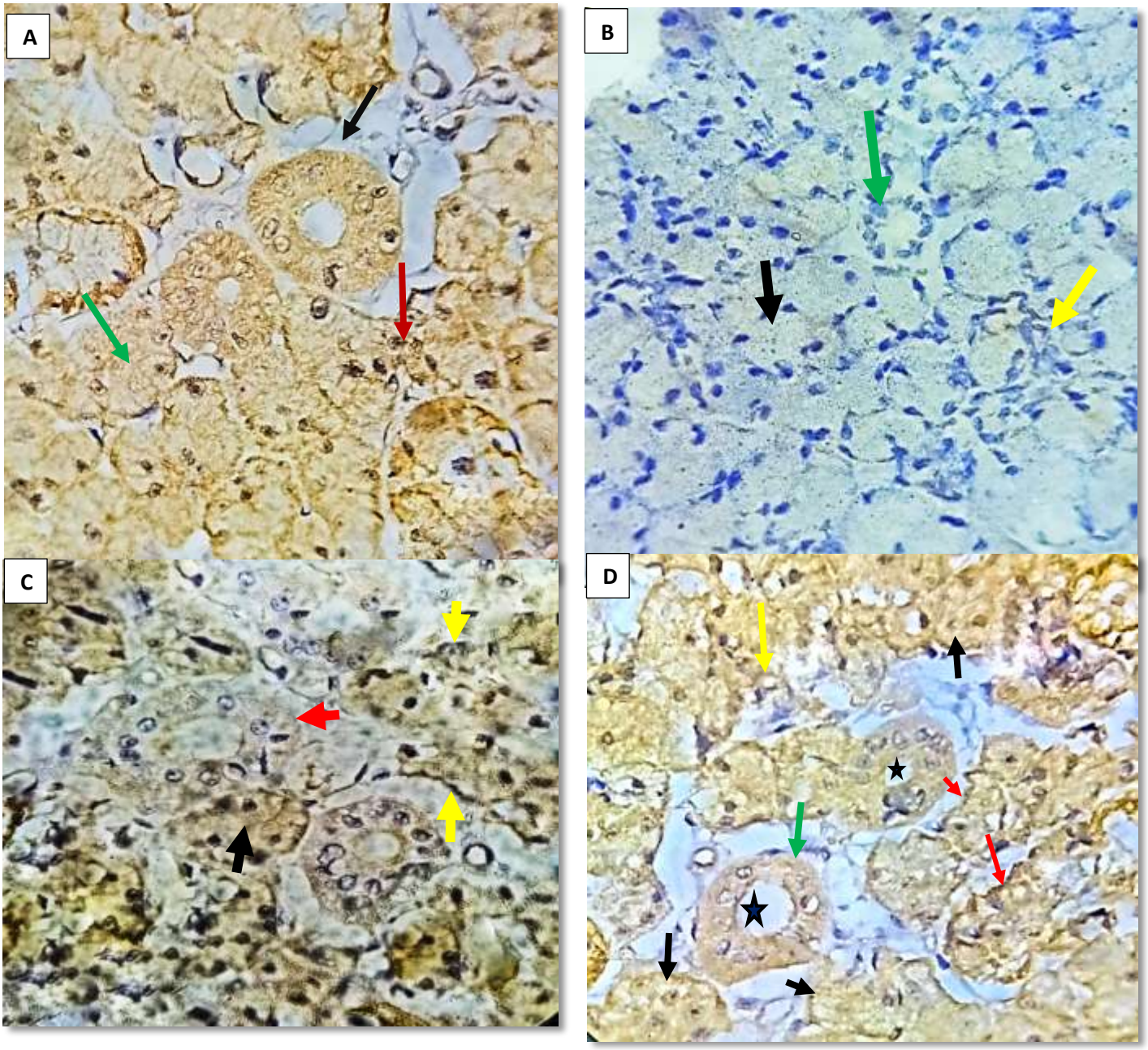

Fig. 3: (A): A photomicrograph of control group showed intercalated (red arrow) and striated ducts (black arrow) with strong to moderate cytoplasmic immunoreaction, Peripheral acinar cells showed moderate

staining (green arrow). **(B):** A photomicrograph of cholesterol group showing negative to week immunoreaction in acinar cells (black arrow), intercalated duct (yellow arrow) and striated duct (green arrow)**. (C):** A photomicrograph of Atorvastatin treated group showing serous acini with moderate immunoreaction (black arrow). moderate staining in myoepithelial cells in the intercalated duct and acini (yellow arrow), striated ducts with moderate cytoplasmic immunoreaction (red arrow)**. (D):** A photomicrograph of ginger+ cinnamon treated group showing serous acini with strong to moderate immunoreaction (black arrow). Peripheral acinar cells showed strong to moderate immunoreaction (red arrows). intercalated (yellow arrow) and striated duct (green arrow) showed strong to moderate immune reaction. Basement membrane of duct cells showed strong to moderate reaction (star) **(VEGF x640)**.

Table (1): Mean Plasma Cholesterol levels of the different experiment groups.

	Before induction of hypercholesterolemia	**At the end of the third month**	**At the end of the fourth month**
Control	97.432	98.857	99.125
Cholesterol rich diet	97.28	165.542	233.525
Cholesterol + Atorvastatin	95.142	166.828	115.202
Cholesterol + Cinnamon+ Ginger	96.000	165.943	113.584

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