



The Antioxidant And Hepatoprotective Effects Of Ginger And Fish Oil On Hypercholesterolemia-Induced Oxidative Stress In Male Rats

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Abstract

The aim of the present study was to investigate the antioxidant and hepatoprotective effects of ginger and fish oil against oxidative stress induced by atherosclerotic diet that enhanced hepatic changes in rats. The animals were divided into four groups of twelve rats each. Group I served as the control. Rats in groups II, III and IV were fed with an atherogenic diet for 8 weeks, group III received atherogenic diet supplemented with 5% ginger, and group IV received atherogenic diet supplemented with 10 % fish oil. Hypercholesterolemia was confirmed by significant elevation of total cholesterol. The protective role of those treatments was confirmed by the significant reduction in the elevated liver enzymes (AST, ALT and ALP levels) and increase in total antioxidant capacity (TAC), catalase (CAT) activity and glutathione reduced (GSH) levels, while malondialdehyde (MDA) levels was significantly reduced when compared with hypercholesterolemic group. We concluded that ginger and fish oil have modulatory effects on antioxidant status and liver functions in hypercholesterolemic male rats.

Key words: oxidative stress, hypercholesterolemia, ginger, fish oil, antioxidant, hepatoprotection

Introduction

Reactive oxygen species (ROS), as well as reactive nitrogen species (RNS) are products of normal cellular metabolism. ROS and RNS are well recognized for playing a dual role as both harmful and beneficial species to living systems (Valko et al., 2007). Increase in production of ROS/RNS on one side and a deficiency of enzymatic and non-enzymatic antioxidants on the other side led to **oxidative stress**. These radicals can induce oxidative damage to cellular lipids, proteins, or DNA inhibiting their normal function. Cell damage caused by free radicals appears to be a major contributor of many diseases (Valko et al., 2007). Hypercholesterolemia is a metabolic disorder characterized by high serum levels of cholesterol and LDL-c (Akinyemi et al., 2015). Hypercholesterolemia was associated with oxidative modification of LDL, protein glycation, glucose-autooxidation, thus leading to excess production of lipid peroxidation products which may cause elevation of oxidative stress in hyperlipidemia (Yang et al., 2008). Hypercholesterolemia has been shown to negatively affect oxidative stress biomarkers and promotes production of reactive oxygen species (ROS) by various mechanisms (Otunola et al.; 2014). There are evidences that low-density lipoprotein (LDL) exposure and cholesterol overload could induce cellular and tissue damages (Lu et al., 2011). According to several reports, controlling ROS is believed to be more

effective in preventing cardiovascular diseases with more potential for success than restrictive fat and cholesterol diet (Otunola et al.; 2014). Recently, there is growing evidence of the protective biochemical functions of naturally occurring antioxidants in biological systems (Olorunnisola et al., 2012). In the search for antioxidant compounds, various concerns are now oriented on many natural products due to their potential to induce antioxidant activity and have various beneficial effects on the biological functions.

Wan, 2013 stated that Hypercholesterolemia can result in nonalcoholic fatty liver disease (NAFLD), which is a pathological condition of emerging clinical importance and considered as the most common cause of abnormal liver function. Omega-3 fatty acids may be effective dietary supplements in the management of various diseases in which oxidant/antioxidant defense mechanisms are decelerated (Erdogana et al., 2004). Fish oil was shown to have beneficial effect on lipid metabolism (Hamadani et al., 2011). It showed significant hepatoprotective activity (Meganathan et al., 2011). Ginger is considered one of the medicinal plants that have many nutritional and functional properties that can affect positively many physiological functions in the body (kumar and Sharma, 2014). The rich phytochemistry of ginger includes components that scavenge free radicals produced in biological systems and led to decrease in lipid peroxidation, so finally

increase of plasma antioxidant capacity. Ginger has hepatoprotective effect due to its strong

Material and methods

Animals and Experimental design

Forty eight mature male Sprague-Dawley rats, of an average body weight 150-200g. Animals were obtained from the animal house, Faculty of Veterinary Medicine, Cairo

Experimental design

Group (I):	12 Rats served as control, maintained on control diet and ad libitum water supply for 8 weeks
Group (II):	12 Rats served as hyperchoestrolemic rats, maintained on atherogenic diet and ad libitum water supply for 8 weeks.
Group (III):	12 Rats served as hyperchoestrolemic rats+ fishoil, maintained on atherogenic diet + 10% fish oil and ad libitum water supply for 8 weeks.
Group (IV):	12 rats served as hyperchoestrolemic rats+ ginger, maintained on atherogenic diet + 5% ginger and ad libitum water supply for 8 weeks

Chemicals

Ginger: Ginger (fine powder) 400 mg. was purchased from Arab Company for Pharmaceuticals & Medicinal Plants (MEPACO-MEDIFOOD) – Egypt. It was added by 5% to diet on the expense of carbohydrates (**Uz et al., 2009**). **Fish oil:** Spring Valley fish **Preparation of atherogenic diet**

antioxidant activity (**El Shemy et al., 2011**).

University. They were housed in plastic cages with wood shaving bedding. Rats were kept for two weeks before the experiment for adaptation with adlibitum feed and water.

oil was purchased from Spring Valley, USA. It was added by 10 % to the diet on the expense of fat (**Sinclair and Gibson. 1992**). **Thiouracil** Thyrocil (propylthiouracil) 50 mg. added to the diet by 0.1%. It was purchased from AMOUN PHARMACEUTICAL CO. S.A.E. – Egypt (**Lin et al., 2017**).

According to **Maruthappan and Shree 2010** . Atherogenic diet was prepared with modification by the addition of bile salts and thiouracil .

Composition	Normal diet (%)	Atherogenic diet (%)
Protein (milk powder)	12	10
Carbohydrates (wheat flour)	71	58.4
Sugar	05	05
Fat (butter)	05	16
Salts	04	04
Vitamins	01	02
Fibers	02	01
Cholesterol	-	01
Bilesalts		2.5
thiouracil		0.1
Total weight	100 g	100 g

Other chemicals

Cholesterol, all vitamins and minerals were obtained from El-Gomhoriya Company, Cairo, Egypt. Bile salts were obtained from El Shark El Awsat Company, Cairo, Egypt. Milk powder, butter, wheat flour, sugar were purchased from the local market

Sampling and techniques

Blood was collected from eye canthus in all rats under light ether anesthesia into heparinized tubes, then these tubes centrifuged for 10 minutes at 4000 r.p.m to obtain plasma. Serum samples also collected and centrifuged for 4000 r.p.m.

Biochemical Measurements

Total antioxidant capacity (TAC) was determined according to the method of **koracevic et al. (2001)**, Lipid peroxide (MDA) was determined according to the method of **Ohkkawa et al., (1979)**, Catalase (CAT) activity was determined according to the method of **Aebi (1984)**, The determination of glutathione reduced was determined according to the method of **Beutler et al. (1963)**. Determination of Total Cholesterol according to the method (**Finley et al., 1978**). Colorometric determination of ALT(Alanine Amino Transferase) and AST

(Aspartate Amino Transferase) according to **Young, 1990** method and ALP (Alkaline Phosphatase) was determined according to **Belfield and Goldberg, 1971**. Kits were purchased from Biodiagnostic company– Egypt.

Histopathological studies

Autopsy samples were taken from liver rats in different groups at the end of experiment and stained by hematoxyline and eosin stain then examination was done by using light electric microscope (**Bancroft et al., 1996**).

Statistical analysis: All data presented as mean±standard error (SE) and were subjected to analysis of variance (ANOVA) test according to **snedecore and Cochran(1980)**. Treatment means were compared by least significant difference test (LSD) at 0.05 levels of probability.

Results

Effect of Ginger and Fish oil on Cholesterol, ,

Table(1):effect of ginger and fish oil on cholesterol, , tac, mda, cat ,gsh ,ast,alt and alp levels in hypercholesterolemic (hyperchol.) Male rats

Control Parameter	Control	Hyperchol.	Hyperchol.+ ginger	Hyperchol.+ fish oil	LSD
Cholesterol (mg/dl)	a 77.8 ±3.6	b 242.5 ±8.6	c 91.5 ±4.4	d 153.9 ±4.6	11
TAC mM/l	a 1.3 ±0.05	b 0.38 ±0.04	c 1.19 ±0.03	d 0.84 ±0.03	0.075
MDA Nmol/ml	a 0.5 ±0.03	b 3.6 ±0.03	c 0.6 ±0.02	d 1.85 ±0.03	0.08
CAT U/L	a 427 ±9.3	b 186 ±5.6	c 396 ±7.7	d 312 ±5.3	14
GSH mg/dl	a 28.75 ±0.84	b 11.75 ±0.85	c 26.75 ±0.94	d 20.25 ±0.68	1.76
AST (U/ml)	a 51.5 ±1.5	b 100.75 ±2.1	c 57.5 ±1.4	d 64.33 ±1.2	2.9
ALT (U/ml)	a 37.92 ±1.7	b 69.3 ±2.4	c 38.7 ±1.2	d 47.7 ±1.1	3.1
ALP (IU/L)	a 99.58 ±2.5	b 181.75 ±4.3	c 108.25 ±2.1	d 122.83 ±1.6	4.9

Means ± S.E, (N) number of rats/group=12, Means within the same row having different superscript letters are significantly different at P < 0.05

TAC, MDA, CAT , GSH , AST, ALT and ALP concentration in hypercholesterolemic male rats

Data presented in table(1) revealed that the lowest TAC , CAT and GSH levels were recorded in hypercholesterolemic male rats , while MDA and cholesterol levels were significantly elevated when compared with treated groups and even control group. Upon supplementation of atherogenic diet with ginger and fish oil antioxidant status was significantly ameliorated when compared with hypercholesterolemic group. As these groups showed significant decrease in cholesterol and MDA levels. Moreover, TAC, CAT and GSH levels were significantly elevated if compared with hypercholesterolemic rats at P < 0.05.

On the other hand, AST,ALT and ALP activities were markedly elevated in hypercholesterolemic group and with ginger and fish oil supplementation these enzymes were significantly diminished at P < 0.05.

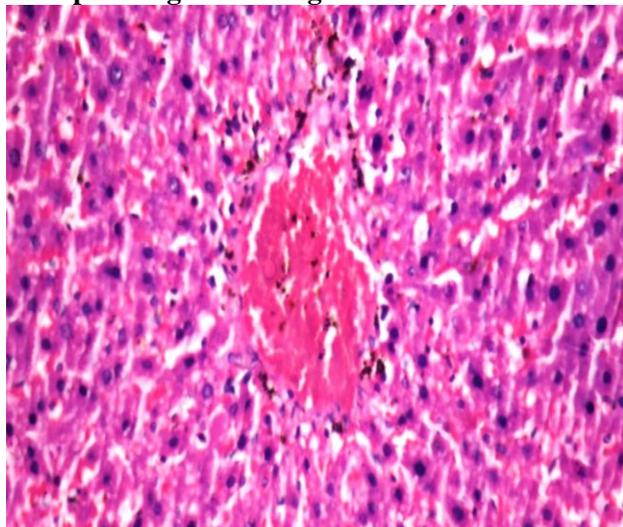
Histopathological findings

Fig.1 (Control group): Liver showing apparently normal hepatic cords and blood sinusoids (H&E X 400).

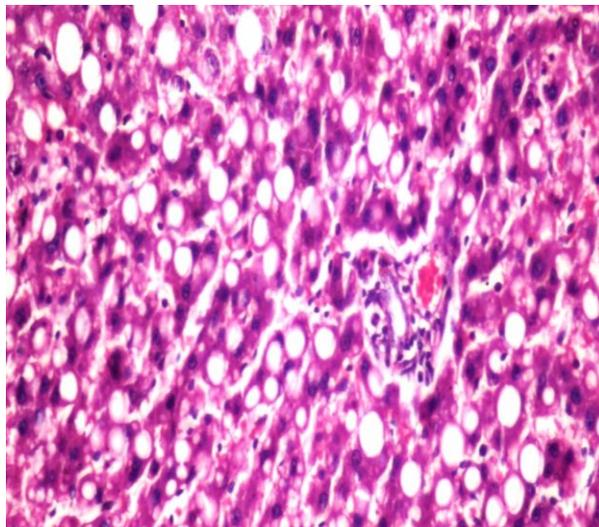


Fig.2 (hypercholesterolemic group): Liver showing fatty degenerated hepatocytes with formation of circumscribed vacuoles with signet ring appearance (H&E X 400).

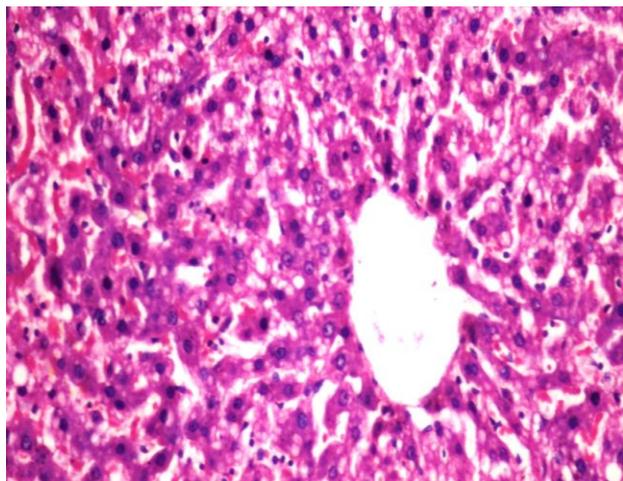


Fig.3 (Hyperchol.+ ginger): Liver showing dilated blood sinusoids and almost no fatty degeneration (H&E X 400).

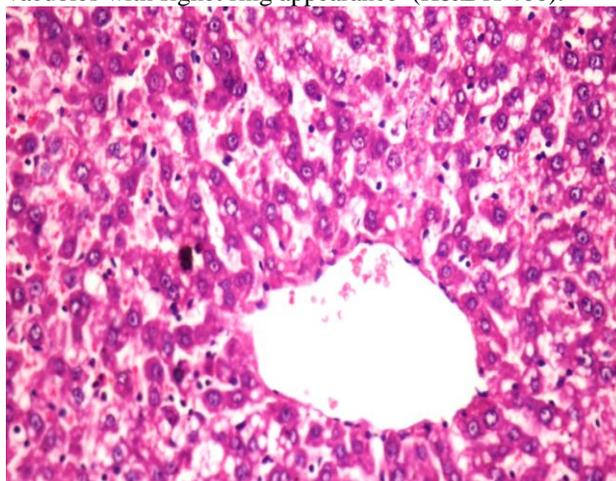


Fig.4 (Hyperchol.+ fish oil): Liver showing dilated blood sinusoids and few atrophied hepatocytes (H&E X 400).

Discussion

In the present study, atherogenic diet feeding for 8 weeks was chosen as the experimental model of hypercholesterolemia. High fat diet containing 1 % cholesterol + 0.25 % bile salts was able to increase total cholesterol and LDL-C in Sprague Dawley rats likely by attenuate bile acid production. Propylthiouracil inhibits thyroid hormone by blocking iodine oxidation resulting in decrease of lipid metabolism. Propylthiouracil was given to ensure atherogenesis in Sprague-Dawley Rats (**shyam et al., 2010**).

Data presented in this study revealed that significant reduction in total antioxidant capacity (TAC), catalase (CAT) activity, and glutathione

reduced (GSH) levels, while malondialdehyde (MDA) levels significantly elevated if compared with control and all treated groups. In addition, AST, ALT and ALP activities was significantly accelerated in comparison with control and treated groups. These results found to be in accordance with **Makni et al.(2008)**, they recorded that in hypercholesterolemic diet, liver is the primary organ to metabolize the excess cholesterol ingested and subjected to oxidative stress firstly. This stress arises from an imbalance between the free radicals production and effectiveness of antioxidant defense system. Increased oxidant stress is suggested to play a critical role in the chronic inflammatory

responses to hypercholesterolemia and atherosclerosis. Thus oxidative stress leads to cell membrane destruction which is related to the free radicals injury and lipid peroxidation (Makni et al., 2008). Enhancement of TBARS levels is an indicator of lipid peroxidation, in animals fed with a high cholesterol diet has been previously reported (Visavadiya and Narasimhacharya, 2007). In addition, hypercholesterolemic rats recorded significant decrease in the activities of the antioxidant enzymes SOD, CAT and GPx, compared to those of control rats. Such inhibition may be attributed to the production of unsaturated aldehydes during lipid peroxidation. These compounds are able to promote oxidative stress by induction of the glutathione cellular consumption and by inactivating selenium-dependent glutathione peroxidase (Makni et al., 2008). Furthermore, hypercholesterolemia was associated with an elevation of the serum and aortic MDA levels, suggesting increase of oxyradicals production, that may be due to enhancement generation through arachidonic acid metabolism for synthesis of prostaglandins and leukotrienes and through WBCs. Increased levels of oxyradicals mitigate endothelial cell injury (Lee and Prasad, 2003).

AST and ALT are cytosolic enzymes, while ALP is a membrane bound enzyme which are mainly found in the liver and kidney and are abnormally found in higher quantities in the serum when the cell membrane is damaged and becomes leaky or even completely ruptured. The high levels of Aspartate and Alanine aminotransferases in the serum is considered an index of organ damage, as it was suggested that deposition of fats in hepatocytes could have been caused by the hypercholesterolemic diet which may lead to cell damage and leakage of these enzymes (Olubunmi, 2011).

Renugadevi et al. (2010) stated that changes in the activities of the liver specific enzymes AST, ALT, and ALP have been recorded as a tool to study cell viability and cell membrane permeability and are the well-known markers of liver cell and tissue damage. Hypercholesterolemia has been considered a risk factor for hepatic injury, several studies on rats and rabbits showed intense deposition of lipids in hepatic areas after feeding with cholesterol enriched diet. This significant

elevation in AST, ALT and ALP may be an indicator of hepatic injury following high cholesterol diet (Keskin et al., 2015). Hepatic histology of the rats fed hypercholesterolemic diet presented in fig.2 showed deposition of lipid and associated with increased production of ROS, often leading to greater hepatic lipid peroxidation (Morán-Ramos et al., 2012).

Ginger treatment results in significant elevation of TAC, CAT and GSH. In addition, ginger supplementation showed significant decrease in the activity of AST, ALT and ALP enzymes comparable with hypercholesterolemic group. The observed decrease in activity of these enzymes after treatment with ginger powder could have been attributed to the recovery of the organ from the nutritional insult imposed by the hypercholesterolemic diet (Olubunmi, 2011). These results were in accordance with Mallikarjuna et al. (2008), who observed significant improvement in liver enzymes associated with administration of ginger as it showed reduction in liver enzymatic activities. Also it was recorded that ginger ethanolic extract (200 mg/kg) administration orally from day 15 to day 21 along with country-made Liquor (CML) results in significant lowering of AST, ALT, ALP activity and tissue lipid peroxidation (Lebda et al., 2012). Ginger treatment was found to exhibit hepatoprotective effect as recorded by enhancement in the activity of the antioxidant enzyme superoxide dismutase (SOD), and diminished amount of lipid peroxidation against the adriamycin-induced hepatotoxicity in rats. It was shown that ginger has the ability to scavenge free radical by its antioxidant activity, ginger-free phenolic and hydrolysed phenolic fractions exhibited DNA protection by free radical scavenging and inhibition of lipid peroxidation, indicating its potent antioxidant properties (Sakr et al., 2011). Also, these results were in harmony with Liu et al. (2003) who recorded that administration of either 2% or 5% ginger containing diets to hyperlipidemic rats showed increased GSH and decreased plasma lipid peroxide levels. Moreover, Asnani and Verma (2009) reported that ginger significantly inhibited lipid peroxidation via ameliorating the activities of the antioxidant enzymes; superoxide dismutase (SOD), catalase and glutathione peroxidase in rats. In addition, several studies revealed that the

aqueous extract of ginger lowered lipid peroxidation and formation of diene, triene and tetraene conjugates in erythrocyte membrane. Supplementation with ginger can reduce free radical mediated oxidative stress to the cells, the crude gingerol extract was found to have antioxidant activity (**Asnani and Verma, 2009**). Total plasma antioxidant capacity (TAC) showed significant repression in hyperlipidemic and diabetic rats. These results were in parallel with **Mahmoud et al. (2014)**. Administration of ginger to hyperlipidemic and diabetic rats significant enhance (TAC) concentrations associated with significant reduction in plasma malondialdehyde (MDA) concentration .also these could be explained that may due to lowering lipid levels. It is known that hyperlipidemic states are associated with altered physical properties of cellular membranes, which may facilitate the escape of free radicals from the mitochondrial electron transport chain or the activation of NADPH oxidase (**Yang et al., 2008**). Hepatic histopathological findings in fig.3 showed significant hepatoprotection in the ginger treated group. These was found to agree with (**Poorrostami et al., 2014**). They observed that the liver sections of rats on treatment with hydroalcoholic extract of ginger exhibited significant liver protection.

Results presented in this study showed dietary intake of fish oil lead to significant improvement in antioxidant status and oxidative stress markers with elevation in total antioxidant capacity (TAC) levels , catalase (CAT) activity and glutathione reduced (GSH) levels, while malondildehydes (MDA) levels were significantly reduced, furthermore AST, ALT and ALP activities were diminished significantly ,when compared with hypercholesterolemic untreated group. Poly unsaturated fatty acids (PUFAs) have displayed cytoprotection against lipid peroxidation increasing the levels of several cellular antioxidants such as ascorbic acid, a-tocopherol and reduced glutathione (GSH) levels (**Makni et al., 2008**).

Our results agree with **Atakisi et al. (2013)**. They reported that fish oil provision restores liver enzymes in rats with diethylnitrosamine (DEN) toxicity. N-3 PUFAs was suggested to ameliorate the toxic effects of DEN in part by means of its free radical scavenging activity and may be of therapeutic value in the protection of

liver against toxic effects of DEN. In addition **Moghadamnia et al. (2016)** recorded that Fish oil omega-3 supplementation and thioacetamide showed a significant improvement in liver enzymes (AST, ALT and ALP) compared to the group receiving thioacetamide only. This means that the supplementation of fish oil omega-3 could protect the hepatic tissue against toxic effect of thioacetamide.

EPA (Eicosapentaenoic acid) and DHA (Docosahexaenoic acid) obtained from fish oil showed antioxidant properties and have a beneficial role in overall metabolism. These oil supplementation may counter the liver toxicity at biochemical level as well as at cellular levels because it shares in the repair and regeneration of altered membrane structures due to increased oxidative stress (**Chavan et al., 2013**). Furthermore, **Chen et al. (2012)** documented that Docosahexaenoic acid (DHA) is an essential polyunsaturated fatty acid that has been shown to possess health beneficial effects, including hepatoprotection . This effect could be related to its strong anti-inflammatory and anti-oxidative effects as well as down-regulation of NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells), NF-KB is a protein complex that controls transcription of DNA, cytokine production and cell survival. It is found in almost all animal cell types and is involved in cellular responses to stimuli such as stress, cytokines, free radicals, heavy metals, ultraviolet irradiation, oxidized LDL, and bacterial or viral antigens (**Gilmore, 2006**). The chemoprotective effect of Omega-3 on liver tissue was confirmed by the attenuation of the activities of serum ALT, AST and ALP. These results are consistent with the results of **Attaia et al.(2011)** and **Abdou and Hassan(2014)**.The mechanism of action of Omega-3 can be attributed to its ability to scavenge free reactive oxygen, block their generation, or enhance endogenous antioxidant status, it may lead to inhibition lipid peroxidation and this action helps to stabilize the reactive radicals and preserve the cellular integrity. Also, it prevents the decrement of GSH level suggesting that Omega-3 may provide the protection to the thiol (SH) group of GSH from the reactive radicals (**Abdou and Hassan, 2014**). Very recent researches demonstrated that genes involving oxidative stress and mitochondrial dysfunction were

down-regulated in the fish oil treated group, and this was in line with the changes of hepatic antioxidant enzyme activities (Li et al., 2017).

Histopathological findings in fig.4 showed significant improvement in hepatic histology upon supplementation of atherogenic diet with

Conclusion

We concluded that ginger and fish oil have modulatory effects on antioxidant status (TAC, MDA, CAT and GSH) as they elevates total antioxidant capacity, prevent depletion of reduced glutathione, enhance catalase activity

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المخلص العربي

التأثيرات المضادة للاكسدة و التي أدت إلي حماية الكبد لكل من الزنجبيل و زيت السمك في حالة الإجهاد التأكسدي والمستحدث عن طريق تناول النظام الغذائي عالي الكوليستيرول في ذكور الفئران

ان الهدف من هذه الدراسة هو تناول التأثير العلاجي لكلا من الزنجبيل وزيت السمك وذلك لما لهما من تأثير مضاد للاكسدة و حماية الكبد وذلك في ذكور الفئران المصابه تجريبيا بالإجهاد التأكسدي عن طريق تغذيتهم بنظام غذائي عالي الكوليستيرول و قد أحدثت تغيرات ملحوظة في كبد الفئران. تم تقسيم الحيوانات إلي أربعة مجموعات وكل مجموعة تتكون من اثني عشرة فأرا. كانت المجموعة الأولى هي المجموعة الضابطة ثم تم تغذية بقية المجاميع بالنظام الغذائي عالي الكوليستيرول لمدة ثمانية أسابيع , بينما المجموعة الثالثة تم إضافة 5% من الزنجبيل إلي النظام الغذائي. والمجموعة الرابعة تم إضافة زيت السمك بنسبة 10 % إلي نظامهم الغذائي. قد تم التأكد من ارتفاع الكوليستيرول بارتفاع مستوي الكوليستيرول الكلي في الدم. أدت هذه المعاملات إلي إنخفاض معنوي في إنزيمات الكبد (الانين امينو ترانسفيريز, اسيرتات امينو ترانسفيريز , والفوسفات القاعدي), وزيادة في القدرة الكلية لمضادات الاكسدة ونشاط انزيم الكاتلاز و مستويات الجلوتاثيون وانخفاض معنوي في مستويات المالنديالدهيد بالمقارنة بمجموعة الفئران عالية الكوليستيرول والغير معالجة. قد خلصنا من هذه النتائج الي أن إضافة الزنجبيل وزيت السمك الي النظام الغذائي أدي إلي تحسن في حالة الإجهاد التأكسدي ووظائف الكبد في ذكور الفئران عالية الكوليستيرول.