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Cholesterol: Genetic, Clinical and Natural Implications

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ABSTRACT

Cholesterol is a lipid that has multiple functions. It is of great importance for cell membrane structure and function in vertebrates. Metabolites of cholesterol viz. bile salts, steroid hormones and oxysterols, fulfill important biological functions. Hypercholesterolemia is an important risk factor for cardiovascular diseases. It is caused by an imbalance between cholesterol secretions into the blood and its uptake. This article is totally based on literature survey. The authors clearly explained the types of cholesterol, their functions and actions. They explored the cholesterol at molecular level by considering genes that regulate it. A number of diseases related to cholesterol were also highlighted. Plants products which can reduce the level of cholesterol were also explored. Moreover drugs that reduce cholesterol were also focused upon and the plant products which can act as their alternative were explained. Control of cholesterol through gene expression was also discussed. The aim of writing this article is to create awareness among the readers worldwide regarding the impact of cholesterol on their health. Moreover this article will help to select food items that can reduce the level of cholesterol and thus safeguard health.

Keywords: Cholesterol, Genes related to cholesterol, Diseases, Drugs, Natural foods

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INTRODUCTION

Lipids are water-insoluble cellular components of diverse structure. Fatty acids are carboxylic acids. It possesses hydrocarbon chains ranging from 4 to 36 carbons long. They are also called as hydrocarbon derivatives. In some fatty acids, this chain is un-branched and fully saturated (contains no double bonds); in others the chain contains one or more double bonds, group. Cholesterol, the major sterol in animals, is both a structural component of membranes and precursor to a wide variety of steroids. Cholesterol is one of the lipids. It is an essential component of the cellular membranes determining the fluidity and biophysical properties by lowering the permeability and increasing the compactness. The distribution of this lipid in the membrane is not uniform but it is enriched in micro-domains, the so-called rafts [1]. Cholesterol is required for embryonic and fetal development [2]. Cholesterol is also a source of bioactive molecules such as steroid hormones, vitamin D and bile acids, which in turn can regulate cellular metabolism and both intracellular and extracellular communication. It is also important for signal transduction [3]. It forms a vital part of the membranes of the spinal cord, nervous system, peripheral nerves and the brain. It is the main constituent of myelin sheath that functions as an insulation layer. Cholesterol is also a forerunner of important hormones such as testosterone, estradiol.

Cholesterol homeostasis is a matter of vital importance in animal physiology, and perturbations in its normal levels have been associated with diseases such as atherosclerosis, diabetes and Alzheimer's disease [4]. Disorders in lipid (e.g., cholesterol and triglycerides) and lipoprotein metabolism are major established independent risk factors in the development and progression of atherosclerotic CHD.

Cholesterol is essential but excess of it leads to deposition in the blood arteries and constricts them leading to blockage and ultimately heart stroke. The deposition of cholesterol in blood arteries leading to the formation of plaque and obstructing blood flow has been explained in the figure 1.

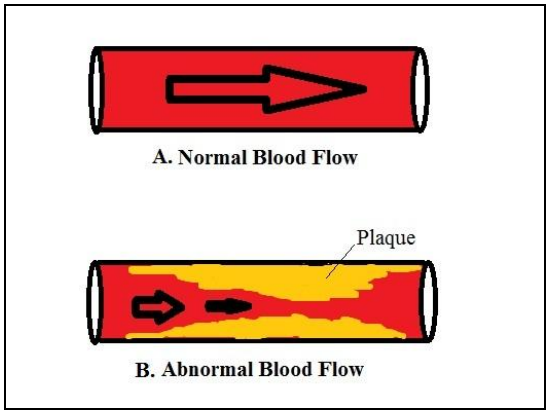

Fig1: Blood flow in human. A. The blood flows is continuous in normal circumstances. **B.** The flow of blood gets obstructed due to plaque formation in the artery.

The main factors responsible for high cholesterol levels are hereditary factors, stress, smoking, obesity and dietary cholesterol. Cardiovascular diseases (CVDs) are the major killers of people globally and around 30 per cent of the total deaths worldwide is due to CVDs [5]. The total number of deaths is projected to reach 23.3 million by 2030 [6]. As per

the data given by WHO, 42 per cent of the total deaths in Egypt is due to CVD. It contributes 38 per cent in case of USA and 28 per cent in India.

This review article is totally based on literature survey. The authors did the literature survey based on modern methods. They took the help of various search engines like science direct, PubMed and Google scholar. Books and journals were also used in the survey. The literatures of the past five years were focused. Others important literatures of the past were also considered. Literatures that have been used in making this article are not restricted to a particular geographical area but were taken from across the globe.

As the corresponding author of this article has the knowledge of biochemistry, molecular biology and biotechnology he tried to explore the cholesterol in a very systematic manner. This review article will summarize current knowledge about the cholesterol. The authors focused on the physical and chemical nature of the cholesterol. They also focused on the biosynthesis of cholesterol. All the types of cholesterol were deeply studied. There functions were highlighted and their impacts on human health were explored.

Communicable diseases represent a worldwide problem as reported by the corresponding author of this article [7]. Moreover the corresponding author along with the other authors also reported that the infectious disease is the cause of morbidity and mortality worldwide [8]. The corresponding author alone has reported his finding on typhoid which comes under infectious diseases [9-13]. In this article the authors described about the cholesterol in case of infectious diseases such as typhoid. Moreover the corresponding author of this article reported about the various technologies related to gene transfer in animals and also in plants [14-17]. In this article he along with the other authors explored the genes in concerned with cholesterol. A numbers of genes were described that regulates cholesterol. In addition to this the corresponding author also reported plant product to be used against typhoid [18-22]. In this article the authors did an exhaustive survey and presented a number of plants product that have potential to decrease the level of cholesterol in blood. Moreover the authors also surveyed the drugs used to decrease the cholesterol. The interesting thing about this article is that the authors have tried to replace the drugs used to decrease cholesterol with plants products. This article reviews recent major efforts towards understanding the importance of cholesterol in day to day life and also to safeguard one self against the demerits of cholesterol. The main aim of writing this article is to create awareness in the mind of people globally regarding the impact of cholesterol on human health so that to reduce the risk of life. The genes related to cholesterol were also explored so to make the study easy for the biotechnologists. Moreover this article also focuses on how to lead a good life with minimal dependence on the drugs.

Physical and chemical nature

Cholesterol is also known by few other names such as Cholesterin, Cholesteryl alcohol, Cholestrin, Cordulan, Dusoline, Dusoran, Provitamin D and Cholesterine.
It is an amphipathic sterol present in higher animals. It's a waxy lipid and distributed in body tissues. Cholesterol can be toxic in the form of polar lipid [3]. Its molecular formula is $C_{27}H_{46}O$ and molecular weight is 386.65354. The IUPAC name of cholesterol is

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(3S,8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-[(2R)-6-methylheptan-2-yl] 2,3,4,7,8,9,11,12,14,15,16, 17-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol. The melting point of cholesterol is 140°C and its specific gravity ranges from 1.06 to 1.07. Cholesterol is minimally soluble in water but insoluble in blood. It is solubilized by its combination with either phospholipids or bile acids. The major part of total cholesterol present is synthesized by the liver and other tissues and a small amount is absorbed in the diet from animal derived foods. It's stored in the cell in the form of cholesterol esters. It's a source of biologically active molecules such as steroid hormones (cortisol, cortisone, aldosterone and progesterone), cholecalciferol (vitamin D) and bile acids [3].

Biosynthesis of Cholesterol

The liver and intestines are the sites where the cholesterol can be synthesized. The biosynthesis in liver and intestines contribute to ten and fifteen per cent, respectively, of the amount produced per day. The synthesis takes place in the cytoplasm and microsomes from the acetate group of acetyl-CoA. The acetyl CoA is derived from oxidation reaction in the mitochondria and then carried to the cytoplasm. The cofactor NADPH is involved in all the reactions of cholesterol biosynthesis. The formation of HMG-CoA ultimately leads to the conversion of Acetyl-CoA to mevalonate. The whole process is summarized in the Fig2.

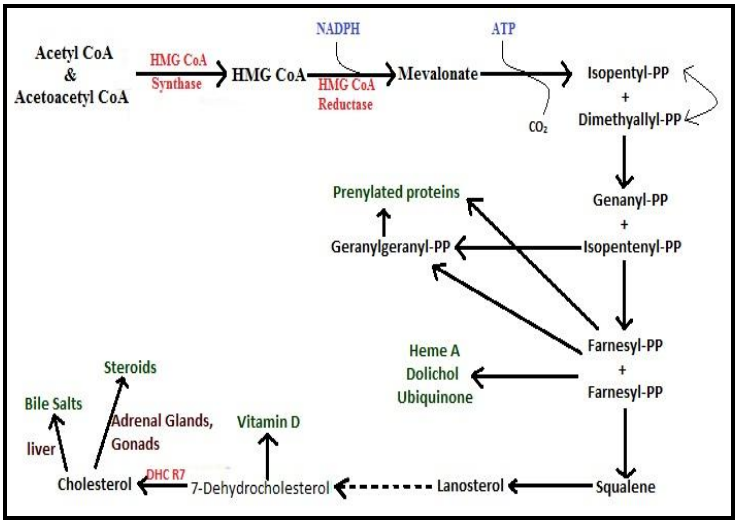

Fig2. Biosynthesis of Cholesterol: Acetyl CoA leads to the formation of HMG CoA which gets converted into mevalonate which in turn forms Isopentenyl pyrophosphate (IPP) accompanied by loss of CO_2. IPP molecules get converted into squalene which in turn forms cholesterol.

Types of Cholesterol

Cholesterol travels within the body by forming a complex with some proteins which are termed as lipoproteins. A lipoprotein is an association of protein and lipids and it exists in combination with proteins in order to allow fats to move across the cell. The protein component plays a part in emulsification of fat molecules. Some examples of lipoproteins include enzymes, transporters, structural proteins, antigens, toxins and adhesins. Depending on the ratio of fat to protein content, lipoproteins can be classified as low density lipoprotein (LDL) which is known as bad cholesterol, high density lipoprotein (HDL) termed

as good cholesterol and very low density lipoprotein (VLDL) which is similar to LDL and triglycerides .

Low Density Lipoproteins

Low density lipoproteins (LDL) or Bad cholesterol, as they are widely known, are lipoproteins which transport cholesterol from liver and intestine to the cells and tissues of the body through bloodstream. They play a vital role in the transfer of cholesterol and metabolism. The density of these particles lies in the range 1.019-1.063 g/ml [23]. A protein known as apolipoprotein B-100 that contains 4536 amino acid residues is present in each LDL particle. The diameter of each LDL particle is around 22 nm and the hydrophobhic core consists of linoleate and esterified cholesterol molecules. A copy of apolipoprotein B-100 and phospholipids are present in the surface monolayer. The major components which constitute LDL molecule are represented in Table 1.

Table 1. Components of LDL

S.No	Components	Composition	Reference
1.	Phosphatidylcholine	450 molecules/ LDL particle	[23]
2.	Sphingomyelin(SM)	185 molecules/LDL particle	[23]
3.	Lysophosphatidylcholine (lyso-PC)	80 molecules/LDL particle	[23]
4.	Phosphatidylethanolamine (PE)	10 molecules/LDL particle	[23]
5.	Diacylglycerol (DAG)	7 molecules/LDL particle	[23]
6.	Ceramide (CER)	2 molecules/LDL particle	[23]
7.	α-tocopherol	6 molecules/LDL particle	[23]

Other than these listed components, some other constituents such as phosphatidylinositol, γ-tocopherol, carotenoids, oxycarotenoids and ubiquinol-10 are also present in minute amounts. There are some subtype patterns of LDL among which those having size in the range 19.00 to 20.50 nm are categorized as Pattern B and those with sizes of 20.6 to 22 nm were kept under the category of Pattern A. The concentration of LDL with their effects is listed in the table 2.

Table 2. Reference chart for LDL levels

S.No	Concentration (mg/dL)	Inference
1.	25 to less than 50	Optimal level which are observed in healthy young children prior to the onset of atherosclerotic plaque in the artery walls of the heart
2.	<70	Nearly optimal level which is observed in condition of advanced symptomatic cardiovascular disease
3.	<100	Sub-optimal level which corresponds to lower rates of symptomatic cardiovascular disease
4.	100-130	Higher chances of developing symptomatic cardiovascular diseases.
5.	130-160	It relates with much higher chances of symptomatic cardiovascular disease.
6.	160-200	Alarming level corresponding to almost certain symptomatic cardiovascular disease event.
7.	>200	Highest risk of developing symptomatic cardiovascular disease.

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High Density Lipoprotein

High density lipoprotein or HDL as it is commonly known is the good cholesterol which carries cholesterol from the cells and tissues to the liver and thus it reduces cholesterol in the blood. These are also known as alpha-lipoproteins or heavy lipoproteins because of their small size and high density. They increase in size by the uptake of cholesterol while circulating through bloodstream. This uptake is known as reverse cholesterol transport which has been depicted in fig3.

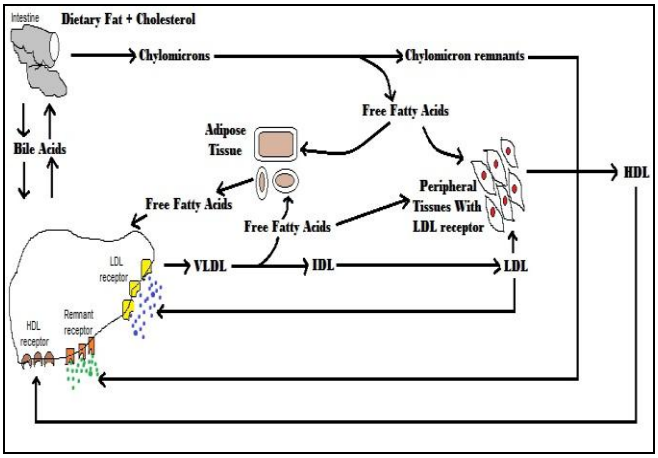

Fig3. Lipoprotein Particle Metabolism: The dietary fat gets metabolized after it enters intestine and then liver brings about the subsequent steps of the metabolism. The process is mediated by receptors for HDL, LDL and chylomicron remnants.

This transport leads to retrieval of cholesterol from other tissues of the body and return it to liver for excretion as bile or in the feces. It has been reported that HDL has a genetic basis too and thus its role in the prevention of heart diseases is also guided by the genetic makeup of an individual [24]. Some other factors include the size of HDL particles and other proteins in the blood. Another important fact is that even though HDL levels correlate with good cardiovascular health but specifically increasing its levels may not lead to a better cardiovascular health [25]. The recommended levels of HDL have been represented in table3.

Table 3. The recommended levels of HDL

S.No	HDL Level (mg/dL)	Inference	Reference
1.	Less than 40 for men Less than 50 for women	High risk of heart diseases	[26]
2.	40-59	Normal HDL levels	[26]

Very Low Density Lipoprotein

Very low density lipoprotein or VLDL is a type of lipoprotein with the highest amount of triglycerides and it is categorized as a type of bad cholesterol because it eventually gets converted into LDL and causes buildup of cholesterol on the walls of arteries [27]. VLDL

plays a role in transport of triglycerides from the liver to the peripheral tissues for storage. Most of the plasma triglyceride is carried by VLDL and thus the levels of VLDL triglycerides and plasma triglycerides are almost the same. VLDL contains apolipoprotein B-100, apolipoprotein C1, apolipoprotein E, cholesterol, cholesteryl esters and triglycerides when it is released from the liver and then it picks up apo C-II and apoE from HDL to become mature VLDL.The normal range for VLDL cholesterol is 2-30 mg/dL and higher levels are associated with stroke and heart diseases.

Triglycerides

Triglycerides are a type of fat present in the body. A triglyceride molecule is basically an ester which constitutes a glycerol molecule bound to three fatty acids. The excess calories which lie unused by the body get converted to triglycerides and then these are stored in the fat cells. Thus triglycerides are the chemical form in which food remains within the body. Then at later stages hormones release these triglycerides for energy between the meals. As per the guidelines given by American Hearts Association (AHA), triglyceride levels should be maintained at a level of less than 150 mg/dL. Increased levels are associated with occurrence of coronary heart diseases [28].

Genes associated with cholesterol disorders

Gene is a segment of nucleic acid that encodes a functional protein or RNA and is the unit of inheritance as described by the corresponding author [16-17]. Recombinant DNA technology has brought about a complete revolution in the way living organisms are utilized. This is achieved by transferring new DNA sequences into animals or by removing or altering DNA sequence in the genome as reported by the corresponding author [16]. He also reported in his article about gene transfer technologies. In this article the authors explained the aspects of cholesterol at molecular level. The authors have done an exhaustive survey and tried to explore a number of genes in concerned with cholesterol.
Cholesterol is delivered to the cells of the body through bloodstream. A mutation in LDLR gene will result into familial hypercholeresterolaemia which is characterized by non-absorption of LDL cholesterol and its circulation in blood. The other genes responsible for hypercholesterolemia are APOB, LDLRAP1 and PCSK1 [29]. The advancements made in genotyping technology have unveiled the genetic mechanisms behind cardiovascular diseases and several candidate genes have been identified which are involved in these disorders. Even though there are environmental factors too which influence the outbreak of cardiovascular disorders but the majority of such diseases are because of mutation in the genes [29-30].

LDLR

LDLR is one of the vital genes required for cholesterol regulation. Some other roles of this gene are cholesterol homeostasis, lipid metabolism, lipid transport, VLDL receptor activity, lipoprotein binding and transmembrane signaling receptor activity. The proximal region of the 3' UTR of LDL receptor mRNA possess vital regulatory sequences which are involved in controlling the messenger stability and they mediate berberine induced increase in LDLR mRNA half-life [31]. Hypercholesterolemia is an autosomal dominant disorder

caused by a mutation in LDLR. The LDL-R synthesis dysfunction of familial hypercholesterolemia patients leads to arterial stenosis and calcification. LDL gets attached to the receptor sites on the targeted cells and get absorbed. The production of these receptors is controlled by LDLR gene present on chromosome 19 at position 13.2 in human beings. This gene family includes cell surface proteins involved in receptor-mediated endocytosis of specific ligands [32]. The gene brings about combination with LDL particle and its excretion outside the cell by endocytosis. The LDL particle is taken up by the cell and it reaches lysosomes.

APOB

APOB gene is located on chromosome 2 between positions 24 and 23. Apolipoprotein is the main protein constituent of chylomicrons, LDL and VLDL. It acts as a recognition signal which brings about the cellular binding and internalization of the LDL particles by apoB/E receptor. The gene APOB codes for the main apolipoprotein of LDLs and it has two isoforms viz. ApoB-48 which is synthesized in the gut and the second one apoB-100 is synthesized in the liver. The N-terminal sequence is common in both the isoforms. ApoB-48 is shorter in length and it is produced after the RNA editing of apoB-100 at residue 2180, which results in a stop codon and early termination of translation. ApoB-48 shares 48% similarity with the sequence of apoB-100. A mutation in this gene is responsible for hypercholesterolemia and other diseases that affect plasma cholesterol and apoB levels. The major polymorphisms include insertion and deletion polymorphism within the coding region of the signal peptide of apoB and it is associated with the risk of coronary heart diseases and myocardial infarction. [33]. High levels of apoB can lead to plaques that are responsible for atherosclerosis. There is one apoB-100 per LDL particle thus LDL can be quantified using apoB-100 concentration.

PCSK9

The proprotein convertase subtilisin/kexin type 9 (PCSK9) gene is located on chromosome 1 at position 32.3 in human beings and it encodes a polyprotein convertase NARC1 which belongs to the proteinase K subfamily of the secretory subtilase family. This protein is synthesized in the form of a soluble zymogen which encounters autocatalytic intramolecular processing in the ER. It is basically a serine protease that decreases the levels of both hepatic and extrahepatic LDL and VLDL receptors [34]. Overexpression of this gene has been linked to decreased levels of LDL receptors (LDLR) because of degradation of the mature receptors [35]. Mutations in this gene are associated with a third form of autosomal dominant hypercholesterolemia. Geneticists are evaluating the methodology to maintain the LDL levels by inhibiting PCSK9 gene [36]. The hepatic expression of LDLR protein increases due to inactivation of PCSK9 gene and it accelerates clearance of circulating LDL and it results into reduced plasma cholesterol [37].

LDLRAP1

LDLRAP1 is located on the short arm of chromosome 1 in case of human beings. This gene is involved in the production of a cytosolic protein which removes cholesterol from bloodstream. This protein has a phosphotyrosine binding domain which interacts with

cytoplasmic tail of the LDL receptor. It is required for both internalization of the LDL-LDLR complex as well as effective binding of LDL to the receptor. In the absence of LDLRAP1 protein LDL receptors fail to effectively remove LDL particles from bloodstream and thus these LDL particles remain in the blood. Thus, a mutation in LDLRAP1 gene will lead to increased levels of LDL in blood which will get deposited in the coronary arteries. This ultimately leads to the clinical condition known as atherosclerosis. Mutation in this gene results into an extremely rare inherited hypercholesterolemia known as autosomal recessive hypercholesterolemia (ARH) [38].

APOA1

The gene APOA1 is located on chromosome 11 between positions 24 and 23 and it is involved in the synthesis of apolipopretein A-I which is a component of HDL. This apolipoprotein joins with the cell membrane and facilitates the movement of cholesterol and phospholipid from within the cell to outside. HDL is formed when these substances combine with apoA-I outside the cell. APOA1 protein induces cholesterol efflux and it is a cofactor for LCAT (lecithin cholesterolacyltransferase) which forms majority of the plasma cholesteryl esters[38]. ApoA-I brings about cholesterol esterification which converts cholesterol to a form that can get integrated into HDL and get transported through the bloodstream. Mutation in this gene results into an altered APOA1 protein and causes an inherited condition known as familial HDL deficiency in which HDL levels are low in the blood and thus elevated chances of cardiovascular disorders.

ABCA1

The ATP-binding-cassette-transporter-A1 gene is located on chromosome 9 at position 31.1 and it is responsible for the synthesis of proteins which transport molecules across the cell membrane. It acts as a cholesterol efflux pump in the cellular lipid removal pathway [39]. Alterations in ABCA1 gene results into a medical condition termed as familial HDL deficiency which is associated with high risk of cardiovascular diseases before the age of 50 years. If the altered gene is present in two copies then it gives rise to tangier disease which is characterized by buildup of cholesterol in the body tissues leading to impaired cell function. The level of HDL may fall to zero in the patients in some cases.

APOE

The apolipoprotein E gene is located on chromosome 19 at position 13.2 and it codes for apolipoprotein E which complexes with lipids and form lipoproteins. It is vital for the normal catabolism of triglyceride rich lipoprotein components. A mutation in this gene impairs chylomicron and VLDL clearance and thus results into type III hyperlipoproteinemia which is characterized by high levels of plasma cholesterol and triglycerides[40].

LCAT

The lecithin-cholesterol acyltransferase (LCAT) gene is located on chromosome 16 at the position 22.1 and it encodes the lecithin-cholesterol acyltransferase which is an extracellular cholesterol esterifying enzyme responsible for cholesterol transport. This

enzyme is synthesized primarily in the liver and plays a central role in extracellular metabolism of plasma lipoproteins. It converts cholesterol and lecithins (phosphatidylcholines) to lysophosphatidylcholines and cholesteryl esters on the surface of LDLs and HDLs. LCAT also plays a crucial role in reverse cholesterol transport and thus lack of LCAT activity will result into accumulation of free cholesterol in the body tissues [41]. This gene works alongside ABCA1 and APOE and bring about maturation of glial derived nascent lipoproteins. Alterations in LCAT cause Norum Disease which is characterized by improper esterification of plasma cholesterol. The genes and also their roles are summarized in table 4.

Table 4. Genes Associated with Cholesterol Disorders

S.No	Gene	Role	Associated Disorders	Reference
1.	LDLR	Cholesterol homeostasis & transport	Hypercholesterolemia	[31]
2.	APOB	Synthesis of apolipoprotein B	Familial Hypercholesterolemia, atherosclerosis	[33]
3.	PCSK9	Regulation of cholesterol in bloodstream	Familial Hypercholesterolemia	[34]
4.	LDLRAP1	Removal of cholesterol from bloodstream	Hypercholesterolemia	[38]
5.	APOA1	Synthesis of a component of HDL	Familial HDL deficiency	[38]
6.	ABCA1	Acts as a cholesterol efflux pump	Tangier disease	[39]
7.	APOE	Catabolism of triglyceride rich lipoprotein components	Hyperlipoproteinemia type III	[42]
8.	LCAT	Extracellular metabolism of plasma lipoproteins	Norum disease	[41]

Diseases and cholesterol

Salmonella typhi is the causative agent of enteric fever. A severe and protracted hypertriglyceridaemia, decrease in HDL-cholesterol levels and increase in LDL-cholesterol levels in patients with enteric fever at the peak of fever has been reported [43]. Levels of triacylglycerides and cholesterol esters were rapidly elevated while di- and monoacylglycerides appeared in heart muscle after intraperitoneal administration of typhoid endotoxin into mice [44]. Content of total lipids was markedly increased in mice myocardium after intraperitoneal administration of typhoid endotoxins. Concentrations of triacylglycerols, free fatty acids, esterified and free cholesterol were mainly altered as reported by the other researchers [44].

Dengu fever is an infectious disease caused by virus. Genetic and pharmacological modulation of cholesterol biosynthesis can regulate dengue virus replication [45]. Lipid profile changes in case of dengue infection. Lowest cholesterol, VLDL levels are the highest in Dengue Shock Syndrome and [46]. Changes in the plasma lipid profile as a potential predictor of clinical outcome in dengue hemorrhagic fever has been reported [47].

HIV is an infectious disease. Lipid abnormalities are common in treatment-naïve HIV-infected patients even in the absence of major host-related risk factors for dyslipidemia.

HIV-infected patients should, therefore, be routinely screened for lipid disorders before commencement of anti-retroviral therapy [48]. Cholesterol involvement in the pathogenesis of neurodegenerative diseases have also been studied by the researchers [49]. Coronary heart disease is a world-wide health care problem. Cholesterol is a major risk factor for the development of coronary heart disease [50]. The authors considered a number of diseases and surveyed the level of cholesterol and summarized it in the table 5

Table 5: Alteration in lipid profile in diseased condition.

S.No.	Diseases	Change in lipid profile	References
1	Cancer	Redued LDL Reduced HDL	[51-53]
2	Severe Dengue	Redued LDL Reduced HDL	[47]
3	Severe Malaria	Raised LDL Raised HDL Reduced triglycerides	[54]
4	Typhoid	Raised LDL Reduced HDL Reduced triglycerides	[55]
5	Post-polio	Raised LDL Raised HDL Raised triglycerides	[56]
6	Alzheimer's Disease	Raised LDL Raised HDL Raised triglycerides	[57]
7	Advanced Tuberculosis	Reduced LDL Reduced HDL	[58]
8	Hepatitis C	Lower LDL Lower HDL	[59]
9	Measles	Lower LDL Lower HDL	[60]
10	Autism	Abnormally low LDL Abnormally low HDL	[61]
11	Influenza A	HDL loses its anti-inflammatory properties	[62]

Impact of food on cholesterol

After the advent of medical science, drugs are available for almost all the disorders and cardiovascular disorders are not an exception. But the common fact which still withholds is that prevention is better than cure and in this context modifying one's food habits is one of the simpler ways to counter the problem of cholesterol. Nature has provided us numerous options for this purpose and we just need to adopt those food items in our lifestyle in order to have a healthy living. Several food crops have shown cholesterol lowering potential; for e.g. lime treated maize husk supplements reduce plasma LDL levels in hypercholesterolemia people [63-64]. Oats is a wonder food item and it is highly efficient in reducing cholesterol levels, its mechanism of action has been depicted in fig.4.

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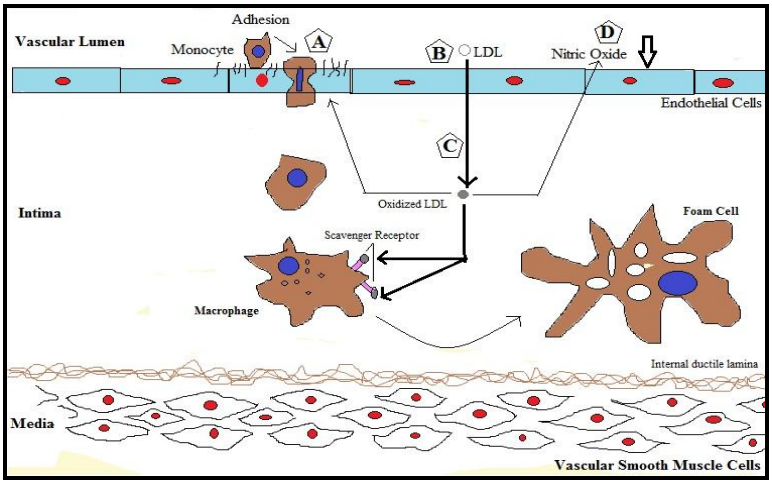

Fig4. Mechanism of cholesterol reduction by Oats. A. Polyphenols present in oats causes reduction in total number of adhesion molecules on the endothelial surface. **B.** Oats reduce chances of LDL entrapment in the vascular wall. **C.** Oats prevent LDL oxidation and scavenge reactive oxygen species **D.** Oats preserve the production of NO and thus inhibit endothelial dysfunction.

The corresponding author of this article Khan reported that the medicinal plants are the backbone of traditional medicine [65]. He explored and reported plants products against diseases [18-22]. Khan also reported that the majorities of the diseases occurs mainly due to the imbalance between prooxidant and antioxidant homeostatic phenomenon in the body [11]. The authors explored the plants and its products to be consumed to reduce cholesterol. Several other such natural cholesterol controlling agents have been represented in Table 6. Moreover the day to day use of cereals and their relation with regards to cholesterol has been listed in the table 7. In addition to this saturated fatty acids contents of animal food is listed in table 8.

Table 6. Food items capable of maintaining cholesterol levels

S.No.	Food Item	Impact on Cholesterol	Components Responsible	Reference
1	Pomegranate (*Punica granatum*)	Inhibits CuSO4-induced LDL oxidation,Reduced Cholesterol accumulation, Inhibits macrophage foam cell formation, Attenuation of atherosclerosis, Scavenge superoxide anion, hydroxyl and peroxyl radicals	Antioxidants such as flavonoids (anthocyanins), polyphenols (Tannins, Proathocyanidins)	[66-68]
2	Sweet Orange *(Citrus sinensis)*	Increases HDL level. lowers LDL and triglycerides. Prevents LDL oxidation Increases ACTH, corticosterone,aldosterone. Decreases erythrocyte and platelet aggregation.	Flavonoids (hesperidin, naringin), inositol, ascorbic acid	[69-71]
3	Amla (*Emblica officinalis*)	exerts the inhibitory effect of hepatic HMG CoA reductase enzyme activity. Corrects dyslipidaemia. Reduction in LDL,VLDL and triglycerides alongwith a significant increase in HDL. Induces aortic plaque regression.	Tannins(emblicanin A and B, punigluconin, pedunculagin), Flavonoid (rutin)	[72-74]

4	Garlic (*Allium sativum*)	Suppresses LDL oxidation. Raises HDL. Reduces VLDL. Inhibits hepatic cholesterol synthesis. Reduces aortic plaques. Antithrombotic, antilipidemic, hemodynamic, Inhibits Vascular calcification	*S*-ethylcysteine, g-glutamyl-*S*-allylcysteine, g-glutamyl-*S*-methylcysteine g-glutamyl-*S*-propylcysteine, Allicin(Mimics statins), saponins	[75-79]
5	Onion (*Allium cepa*)	Reduces blood triglycerols. Limits hepatic cholesterol biosynthesis. Excrete cholesterol through gastrointestinal tract.	Allicins	[78]
6	Watermelon (*Citrullus lanatus*)	Vasodilator, improves endothelial dysfunction,decreases lipid peroxidation in liver, Attenuation of hypercholesterolemia-induced atherosclerosis	Citrulline	[80-82]
7	Almonds (*Prunus amygdalus*)	Scavenge free radicals. Inhibit copper induced oxidation of LDL. Increase HDL	Fiber, flavonoids,	[83]
8	Apple (*Malus domestica*)	Enhanced fecal excretion of bile acids, hepatic degradation of cholesterol Inhibits ApoB synthesis, Decreased cholesterol Esterification	Polyphenols, Pectin, Flavonoid (Procyanidins)	[84-86]
9	Cranberry *(Vaccinium macrocarpon)*	Inhibit LDL oxidation. Increases reverse cholesterol transport. Decreased risk of atherosclerosis.	Flavonoids (anthocyanins, quercetin, myricetin), hydroxycinnamic acids, polyphenols (proanthocyanidins)	[87-90]
10	Mulberry *(Morus alba L.)*	Inhibits LDL oxidation. Scavenge free radicals. Promotes HDL uptake in liver. Inhibits hepatic lipogenesis. Increases LDL-receptor activity	Flavonoids (anthocyanins, rutin, Phenols, Flavonols (morin, quercetin and myricetin),a-linolenic acid,unsaturated fatty acid (linoleic acid)	[91-93]
11	Grape(*Vitis vinifera*)	Inhibits LDL oxidation ,enhanced reverse cholesterol transport,reduced intestinal cholesterol absorption, Increased faecal excretion of lipids and cholesterol, inhibits platelet aggregation, reduced secretion of ApoB containing lipoproteins	Flavanols (proanthocyanidin, Polyphenol (tannins), Flavonois (naringenin)	[94-97]
12	Banana (*Musa sapienturn*)	Hypocholesterolaemic effect	Soluble and insoluble fibers, flavonoids	[98-99]
13	Tomato (*Solanum lycopersicum*)	Reduces dietary cholesterol absorption. Decreases serum lipid peroxidation and LDL oxidation	Tomatine (a-tomatine and dehydrotomatine), lycopene.	[100-102]
14	Arjun (*Terminalia arjuna*)	Anti-oxidant, anti-ischemic	Polyphenols (gallic acid, ellagic acid), flavonols (catechin, gallocatechin, epigallocatechin)	[103-104]

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Table7: Cereals for controlling cholesterol

S.No.	Cereal	Impact	Reference
1.	Wheat (*Triticum spp.)*	Reduces LDL levels without affecting glucose and insulin metabolism	[105-106]
2.	Brown Rice (*Oryza sativa*)	enhanced the fecal excretion of neutral sterols	[107]
3.	Barley (*Hordeum vulgare*)	Decreased hepatic cholesterogenesis	[108]
4.	Jowar (*Sorghum sp*)	Inhibit HMG CoA Reductase. Increases HDL	[64]
5.	Oats (*Avena sativa*)	Lowers HDL. Carries cholesterol out of the body. Reduction in waistline, atheroprotective	[109-110]
6.	Rye (*Secale cereale*)	Prevents LDL oxidation	[111]
7.	Buckwheat (*Fagopyrum esculentum*)	Increase in HDL levels	[112]
8.	Quinoa (*Chenopodium quinoa*)	Reduces LDL	[113]

Table8. Saturated fatty Acid Content of Edible oils from plant sources

S.No.	Type of oil	Percentage of saturated fatty acids	Reference
1	Mustard oil	0.06 %	[114]
2	Corn Oil	13 %	[114]
3	Coconut Oil	88 %	[114]
4	Soybean oil	15 %	[114]
5	Cottonseed oil	26 %	[114]
6	Palm oil	48%	[114]
7	Olive oil	14 %	[114]
8	Peanut oil	19 %	[114]
9	Sunflower seed oil	10 %	[114]
10	English Wallnut oil	11 %	[114]
11	Safflower oil	9 %	[114]
12	Linseed oil	13 %	[114]

Table 9: Saturated fatty acid content of animal foods

S.No.	Type of Oil	Percentage of saturated fatty acids	Reference
1	Cod liver oil	19 %	[115]
2	Channel catfish oil	26 %	[115]
3	Mackerel	35 %	[115]
4	Whale	19 %	[115]
5	Cow milk fat	62 %	[115]
6	Chicken fat	33 %	[115]
7	Egg yolk	53 %	[115]
8	Beef liver	39	[115]
9	Beef tallow	48 %	[115]
10	Lard	36 %	[115]

Drugs and their alternative natural products to reduce cholesterol

The genetic cause of high cholesterol can be treated by drug therapy. Currently, there are drugs in the pharmaceutical market for this purpose. These drugs acts by binding with the cholesterol present in the intestines and thus preventing it from being absorbed. In other words, these drugs act as scavenger and thus the body begins to utilize more cholesterol to produce bile and ultimately leading to a fall in blood cholesterol levels. It has been reported that wood cellulose lowers cholesterol by about 33 per cent and Hydroxypropyl-methylcellulose (HPMC) lowers it by around 50 per cent [116]. Even though these drugs are capable of maintaining the blood cholesterol levels but there are some better alternatives which can be used as an alternative to these drugs. Statins decrease cholesterol levels by increasing the uptake of LDL, by blocking synthesis of hepatic cholesterol and activating hepatic production of apoA-I. These drugs can be replaced by whole grains, nuts, fatty fish, pure sugarcane and amla [117]. Similarly Niaspan acts by decreasing the fractional catabolic rate of apoA-I without affecting the rate of synthesis and it can be replaced by peanuts, fish and bran [117]. Similarly Gemfibrozil and fenofibrate which induce production of the primary HDL apolipoproteins, apoA-I and apoA-II can be replaced by oats, bran and apple [118]. These drugs also promote positive regulation of lipoprotein lipase activity and thus blocking fatty acid and triglyceride synthesis ultimately leading to a fall in the levels of VLDL and triglycerides. Raisins and grapes can replace the drugs Cholestyramine and Colestipol which act by blocking bile acid synthesis by binding with them and thus inhibiting hepatic reapportion [119]. Another drug Ezetimibe works by blocking the intestinal brush border transporter involved in cholesterol transport and this drug can be replaced by soy protein [120].

Control of cholesterol through gene expression

A newly designated method is to engineer protein expression in order to express LDL receptors. In this method, engineered versions of the LDL receptor were constructed by site-directed mutagenesis of the receptor cDNA and then transfected into fibroblast like COS cells derived from monkey kidney tissue. These cell lines were produced by killing CV-1 cells by SV40 virus which is capable of producing a large T antigen but it has minor defect in the process of genomic replication. Cells were then assayed for their potential to bind with various ligands such as VLDL and LDL after rectifying the variations in cell surface expression levels. Deleting specific cysteine rich repeated elements within the receptor reduces LDL binding. This leads to a better understanding of the critical regions of the protein required for LDL binding. These studies have the promise to treat familial hypercholesterolemia in future [121].

CONCLUSION

In this article the authors explored the cholesterol and made it easy to understand to the readers. All types of cholesterol were discussed separately and their impacts on human health were discussed. The authors also explained the biosynthesis of cholesterol in the body. A lot of genes were explored by the authors and their functions were summarized. The authors also listed a number of drugs used to reduce cholesterol and a number of natural foods used for the same purposes. It is now the duty of the fellow researchers to

come forward and explore the other genes that take part in cholesterol regulation. Moreover they should also try to discover safer drugs that can bring down the cholesterol to normal level. Medicinal plants and natural food should be explored to reduce the cholesterol. Much attention is required to reduce the cholesterol as it is related to cardiovascular disease. The lowering of cholesterol will definitely reduce the rate of blockage, stroke and death rate.

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REFERENCES

[1] Ledesma MD, Abad-Rodriguez J, Galvan C, Biondi E, Navarro P, Delacourte A, Dingwall C and Dotti CG, EMBO Reports, 2003; 4(12): 1190-1196.
[2] Woollett LA, Placenta, 2011; 32(2): S218-S221.
[3] Liu JP, Molecular and Cellular Endocrinology, 2009; 303(1-2): 1-6.
[4] Coreta-Gomes FM, Vaz WLC, Wasielewski E, Geraldes CFGC and Moreno MJ, Analytical Biochemistry, 2012; 427(1): 41-48.
[5] Gersh BJ, Sliwa K, Mayosi BM and Yusuf S, European Heart Journal, 2010; 31(6): 642-648.
[6] Mathers CD and Loncar D, PLOS Medicine, 2006; 3(11): e442.
[7] Khan KH, GERMS, 2013; 3(1): 26-35.
[8] Maurya S, Priya T and Khan KH, International Journal of Science Innovations and Discoveries, 2013; 3(1): 34-48.
[9] Khan KH, International Journal of Biosciences, 2012; 2(3):110-120.
[10] Khan KH, International Journal of Biosciences, 2012; 2(1): 9-17.
[11] Khan KH, Latin American Journal of Pharmacy, 2010; 29(2): 171-177.
[12] Khan KH, Recent Research in Science and Technology, 2010; 2(4): 29-36.
[13] Khan KH, Ganjewala D and Rao KVB, Advanced Biotech, 2008; 7(4): 35-40.
[14] Khan KH, Asian Journal of Experimental Biological Science, 2010; 1(1): 208-218.
[15] Khan KH, Recent Research in Science and Technologies, 2009; 1(3): 116-123.
[16] Khan KH, Journal of Ecobiotechnology, 2009; 1(1): 32-40.
[17] Khan KH, Asian Journal of Experimental Biological Science, 2010; 1(1): 208-218.
[18] Khan KH, Botany Research International, 2009; 2(4): 218-228.
[19] Khan KH and Jain SK, Advanced BioTech, 2009; 8(9): 10-15.
[20] Khan KH, Recent Research in Science and Technology, 2009; 1(5): 211-216.
[21] Khan KH, Advances in Biological Research, 2009; 3(1-2): 1-8.
[22] Khan KH, EurAsian Journal of BioSciences, 2009; 3(15): 113-121.
[23] Hevonoja T, Pentikainen MO, Hyvonen MT, Kovanen PT and Ala-Korpela M, Biochimica et Biophysica Acta, 2000; 1488(3): 189-210.
[24] Weissglas-Volkov D and Pajukanta P, The Journal of Lipid Research, 2010; 51(8): 2032-2057.
[25] Voight BF, Peloso GM, Orho-Melander M, Frikke-Schmidt R, Barbalic M, Jensen MK, Hindy G, Hólm H, Ding EL, Johnson T, Schunkert H, Samani NJ, Clarke R, Hopewell JC,

Thompson JF, Li M, Thorleifsson G, Newton-Cheh C, Musunuru K, Pirruccello JP, Saleheen D, Chen L, Stewart A, Schillert A, Thorsteinsdottir A, Thorgeirsson G, Anand S, Engert JC, Morgan T, Spertus J, Stoll M, Berger K, Martinelli N, Girelli D, McKeown PP, Patterson CC, Epstein SE, Devaney J, Burnett MS, Mooser V, Ripatti S, Surakka I, Nieminen MS, Sinisalo J, Lokki ML, Perola M, Havulinna A, de Faire U, Gigante B, Ingelsson E, Zeller T, Wild P, de Bakker PI, Klungel OH, Maitland-van der Zee AH, Peters BJ, de Boer A, Grobbee DE, Kamphuisen PW, Deneer VH, Elbers CC, Onland-Moret NC, Hofker MH, Wijmenga C, Verschuren WM, Boer JM, van der Schouw YT, Rasheed A, Frossard P, Demissie S, Willer C, Do R, Ordovas JM, Abecasis GR, Boehnke M, Mohlke KL, Daly MJ, Guiducci C, Burtt NP, Surti A, Gonzalez E, Purcell S, Gabriel, Marrugat J, Peden J, Erdmann J, Diemert P, Willenborg C, König IR, Fischer M, Hengstenberg C, Ziegler A, Buysschaert I, Lambrechts D, Van de Werf F, Fox KA, El Mokhtari NE, Rubin D, Schrezenmeir J, Schreiber , Schäfer A, Danesh J, Blankenberg S, Roberts R, McPherson R, Watkins H, Hall AS, Overvad K, Rimm E, Boerwinkle E, Tybjaerg-Hansen A, Cupples LA, Reilly MP, Melander O, Mannucci PM, Ardissino D, Siscovick D, Elosua R, Stefansson K, O'Donnell CJ, Salomaa V, Rader DJ, Peltonen L, Schwartz SM, Altshuler D and Kathiresan S, Lancet, 2012; 380(9841): 572-580.

[26] Shaikh Q and Kamal AK, Journal of the Pakistan Medical Association, 2012; 62(6): 623.

[27] Shelness GS and Sellers JA, Current opinion in Lipidology, 2001; 12(2): 151-157.

[28] Labreuche J, Touboul PJ and Amarenco P, Atherosclerosis, 2009; 203(2): 331-345.

[29] Soufi M, Rust S, Walter M and Schaefer JR, Gene, 2013; 521(1): 200-203.

[30] Levy D, Larson MG, Benjamin EJ, Newton-Cheh C, Wang TJ, Hwang SJ, Vasan RS and Mitchell GF, BMC Medical Genetics, 2007; 8(1): S3.

[31] Chen W, Wang S, Ma Y, Zhou Y, Liu H, Strnad P, Kraemer FB, Krauss RM and Liu J, International Journal of Molecular Medicine, 2008; 21(3): 345-353.

[32] Goldstein JL and Brown MS, Arteriosclerosis, Thrombosis, and Vascular Biology, 2009; 29(4): 431- 438.

[33] Kallel A, Ben Ali S, Sediri Y, Chabrak S, Elasmi M, Sanhaji H, Souheil O, Haj- Taieb S, Feki M, Mechmeche R, Jemaa R and Kaabachi N, Clinical Chemistry and Laboratory Medicine, 2008; 46(8): 1097-1101.

[34] Abifadel M, Varret M, Rabès JP, Allard D, Ouguerram K, Devillers M, Cruaud C, Benjannet S, Wickham L, Erlich D, Derré A, Villéger L, Farnier M, Beucler I, Bruckert E, Chambaz J, Chanu B, Lecerf JM, Luc G, Moulin P, Weissenbach J, Prat A, Krempf M, Junien C, Seidah NG and Boileau C, Nature Genetics, 2003; 34(2): 154-156.

[35] Maxwell KN, Fisher EA and Breslow JL, Proceedings of the National Academy of Sciences of the United States of America, 2005; 102(6): 2069-2074.

[36] Steinberg D and Witztum JL, Proceedings of the National Academy of Sciences of the United States of America, 2009; 106(24): 9546-9547.

[37] Lopez D, Drugs News & Perspectives, 2008; 21(6): 323-330, 2008.

[38] Tada H, Kawashiri MA, Ohtani R, Noguchi T, Nakanishi C, Konno T, Hayashi K, Nohara A, Inazu A, Kobayashi J, Mabuchi H and Yamagishi M, Atherosclerosis, 219(2): 663-666.

[39] Lawn RM, Wade DP, Garvin MR, Wang X, Schwartz K, Porter JG, Seilhamer JJ, Vaughan AM and Oram JF, The Journal of Clinical Investigation, 104(8): 25-R31.

[40] Diaz JA, Ballard-Lipka NE, Farris DM, Hawley AE, Wrobleski SK, Myers DD, Henke PK, Lawrence DA and Wakefield TW, Journal of Vascular Surgery, 2012; 55(3): 815-822.

[41] Haase CL, Tybjærg-Hansen A, Qayyum AA, Schou J, Nordestgaard BG and Frikke-Schmidt R, The Journal of Clinical Endocrinology and Metabolism, 2012; 97(2): E248-E256.
[42] Poirier J, Neurobiology of Ageing, 2005; 26(3): 355-361.
[43] Khosla SN, Goyle n and Seth RK, The Journal of the Association of Physicians in India, 1991; 39(3): 260-262.
[44] Muzhichenko AV and Khardina GA, Voprosy meditsinskoĭ khimii, 1982; 28(2): 39-44.
[45] Rothwell C, Lebreton A, Young Ng C, Lim JY, Liu W, Vasudevan S, Labow M, Gu F and Gaither LA, Virology, 2009; 389(1-2): 8-19.
[46] Suvarna JC and Rane PP, Tropical Medicine & International Health, 2009; 14(5): 576-85.
[47] van Gorp EC, Suharti , Mairuhu AT, Dolmans WM, van Der Ven J, Demacker PN and van Der Meer JW, Clinical Infectious Diseases, 2002; 34(8): 1150-1153.
[48] Daniyam C and Iroezindu M, Annals of Medical and Health Sciences Research, 2013; 3(1): 26-30.
[49] Liu JP, Tang Y, Zhou S, Toh BH, McLean C and Li H, Molecular and Cellular Neuroscience, 2010; 43(1): 33-42.
[50] Rauchhaus M, Clark AL, Doehner W, Davos C, Bolger A, Sharma R, Coats AJS and Anke SD, Journal of the American College of Cardiology, 2003; 42(11): 1933-1940.
[51] Henriksson P, Ericsson S, Stege R, Eriksson M, Rudling M, Berglund L and Angelin B, The Lancet, 1989; 334(8673): 1178-1180.
[52] Kucharska-Newton AM, Rosamond WD, Schroeder JC, McNeill AM, Coresh J and Folsom AR, Lung Cancer, 2008; 61(3): 292-300.
[53] Fuhrman B, Wolfovitz E, Cogan U and Brook GJ, Pathophysiology, 1999; 6(3): 205-210.
[54] Mohanty S, Mishra SK, Das BS, Satpathy SK, Mohanty D, Patnaik JK and Bose TK, Annals of Tropical Medicine and Parasitology, 1992; 86(6): 601-601.
[55] Amal HA and Eman SS, AJPS, 2010; 7(1): 14-22.
[56] Agre JC, Rodriquez AA and Sperling KB, Archives of physical medicine and rehabilitation, 1990; 71(6): 393-394.
[57] Puglielli L, Tanzi RE and Kovacs DM, Nature Neuroscience, 2003; 6(4): 345-351.
[58] Deniz O, Gumus S, Yaman H, Ciftci F, Ors F, Cakir E, Tozkoparan E, Bilgic H and Ekiz K, Clinical Biochemistry, 2007, 40(3-4): 162-166.
[59] Maggi G, Bottelli R, Gola D, Perricone G, Posca M, Zavaglia C and Ideo G, The Italian Journal of Gastroenterology, 1996; 28(8): 436-440.
[60] Shahar R, Dafa-Berger A, Dyer MD, Paeper B, Proll SC, Teal TH, Rom S, Fishman D, Rager-Zisman B and Katze MG, Journal of Virology, 2009; 83(11): 5495-5504.
[61] Tint GS, Irons M, Elias ER, Batta AK, Frieden R, Chen TS and Salen G, New England Journal of Medicine, 1994; 330(2): 107-113.
[62] Van Lenten BJ, Wagner AC, Nayak DP, Hama S, Navab M and Fogelman AM, Circulation, 2001; 103(18): 2283-2288.
[63] Vidal-Quintanar RL, Mendívil RL, Peña M and Fernandez ML, The British Journal of Nutrition, 1999, 81(4): 281-288.
[64] Carr TP, Weller CL, Schlegel VL, Cuppett SL, Guderian Jr DM and Johnson KR, The Journal of Nutrition, 2005; 135(9): 2236-2240.
[65] Khan KH and Jain SK, Hamdard Medicus, 2003; 46(3): 23-33.

[66] Fuhrman B, Volkova N and Aviram M, The Journal of Nutritional Biochemistry, 2005; 16(9): 570-576.
[67] Al-Muammar MN and Khan F, Nutrition, 2012; 28(6): 595-604.
[68] Rosenblat M, Hayek T and Aviram M, Atherosclerosis, 2006; 187(2): 363-371.
[69] Parmar HS and Kar A, Journal of Medicinal Food, 2008; 11(2): 376-381.
[70] Deyhim F, Villarreal A, Garcia K, Rios R, Garcia C, Gonzales C, Mandadi K and Patil BS, Nutrition, 2007; 23(7-8): 617-621.
[71] Cesar TB, Aptekmann NP, Araujo MP, Vinagre CC and Maranhão RC, Nutrition Research, 2010; 30(10): 689-694.
[72] Gopa B, Bhatt J and Hemavathi KG, Indian Journal of Pharmacology, 2012; 44(2): 238– 242.
[73] Mathur R , Sharma A , Dixit VP and Varma M, Journal of Ethnopharmacology, 1996; 50(2): 61-68.
[74] Antony B, Benny M and Kaimal TNB, Indian Journal of Clinical Biochemistry, 2008; 23(4): 378-381.
[75] Yeh YY and Liu L, The Journal of Nutrition, 2001; 131(3): 989S-993S.
[76] Durak İ, Kavutcu M, Aytaç B, Avc A, Devrim E, Özbek H and Öztürk HS, The Journal of Nutritional Biochemistry, 2004; 15(6): 373-377.
[77] Ali M, Al-Qattan KK, Al- Enezi F, Khanafer RMA and Mustafa T, Prostaglandins, Leukotrienes and Essential Fatty Acids (PLEFA), 2004; 62(4): 253-259.
[78] Emmanuel UC and James O, Annual Review & Research in Biology, 2011; 1(3): 37-44.
[79] Singh DK and Porter TD, Journal of Nutrition, 2006; 136(3): 759S- 764S.
[80] Altas S, Kizil G, Kizil M, Ketani A and Haris PI, Food and Chemical Toxicology, 2011; 49(9): 2433-2438.
[81] Figueroa A, Sanchez-Gonzalez MA, Perkins-Veazie PM and Arjmandi BH, American Journal of Heypertension, 2011; 24(1): pp. 40-44.
[82] Poduri A, Rateri DL, Saha SK, Saha S and Daugherty A, The Journal of Nutritional Biochemistry, 2013; 24(5): 882-886.
[83] Jaceldo-Siegl K, Sabaté J, Batech M, and Fraser GE, Nutrition, Metabolism and Cardiovascular Diseases : NMCD, 2011; 21(1): S7-S13.
[84] Sablé-Amplis R, Sicart R, and Agid R, Nutrition Research, 1983; 3(3): 325-328.
[85] González M, Rivas C, Caride B, Lamas MA and Taboada MC, Journal of Physiology and Biochemistry, 1998; 54(2): 99-104.
[86] Vidal R, Hernandez-Vallejo S, Pauquai T, Texier O, Rousset M, Chambaz J, Demignot S and Lacorte JM, Journal of Lipid Research, 2005; 46(2): 258-268.
[87] Ruel G, Pomerleau S, Couture P, Lamarche B and Couillard C, Metabolism Clinical and Experimental, 2005; 54(7): 856- 861.
[88] Reed J, Critical Reviews in Food Science and Nutrition, 2002; 42(3): 301-316.
[89] Sun J, Chu YF, Wu X and Liu RH, Journal of Agriculture and Food Chemistry, 2002; 50(25): 7449-7454.
[90] Zheng W and Wang SY, Journal of Agriculture and Food Chemistry, 2003; 51(2): 502-509.
[91] Chen CC, Liu LK, Hsu JD, Huang HP, Yang MY and Wang CJ, Food Chemistry, 2005; 91(4): 601-607.
[92] Yang X, Yang L and Zheng H, Food and Chemical Toxicology, 2010; 48(8-9).
[93] Venkatesan N, Devaraj SN and Devaraj H, European Journal of Nutrition, 2003; 42(5): 262-271.

[94] Yamakoshi J, Kataoka S, Koga T and Ariga T, Atherosclerosis, 1999; 142(1): 139-149.
[95] Zern TL, West KL and Fernandez ML, The Journal of Nutrition, 2003; 133(7): 2268-2272.
[96] Stein JH, Keevil JG, Wiebe DA, Aeschlimann S and Folts JD, Circulation, 1999; 100(10): 1050-1055.
[97] Shanmuganayagam D, Warner TF, Krueger CG, Reed JD and Folts JD, Atherosclerosis, 2007; 190(1): 135-142.
[98] Horigome T, Sakaguchi E and Kishimoto C, British Journal of Nutrition , 1992; 68(1): 231-244.
[99] Vijayakumar S, Presannakumar G and Vijayalakshmi NR, Journal of Dietary Supplements, 2009; 6(2): 111-123.
[100] Friedman M, Fitch TE and Yokoyama WE, Food and Chemical Toxicology, 2000; 38(7): 549-553.
[101] Silaste ML, Alfthan G, Aro A, Kesäniemi YA and Hörkkö S, British Journal of Nutrition, 2007; 98(6): 1251-1258.
[102] Agarwal S and Rao AV, Lipids, 1998; 33(10): 981-984.
[103] Saha A, Pawar VM and Jayaraman S, Indian Journal of Pharmaceutical Sciences, 2012; 74(4): 339-347
[104] Ali A, Kaur G, Hayat K, Ali M and Ather M, Die Pharmazie, 2003; 58(12): 932-934.
[105] Price RK, Keaveney EM, Hamill LL, Wallace JM, Ward M, Ueland PM, McNulty H, Strain JJ, Parker MJ and Welch RW, The Journal of Nutrition, 2010; 140(12): 2153-2157.
[106] Kothari S, Jain AK, Mehta SC and Tonpay SD, Acta Poloniae Pharmaceutica, 2011; 68(2): 291-294.
[107] Miura D, Ito Y, Mizukuchi A, Kise M, Aoto H, and Yagasaki K, Life Sciences, 2006; 79(3): 259-264.
[108] AbuMweis SS, Jew S and Ames NP, European Journal of Clinical Nutrition, 2010; 64(12): 1472-1480.
[109] Zhang J, Li L, Song P, Wang C, Man Q, Meng L, Cai J and Kurilich A, Nutrition Journal, 2012; 11: 54.
[110] Andersson KE, Svedberg KA, Lindholm MW, Öste R and Hellstrand P, Atherosclerosis, 2010; 212(1): 93-99.
[111] Andreasen MF, Landbo AK, Christensen LP, Hansen Å. and Meyer AS, Journal of Agricultural and Food Chemistry, 2001; 49(8): 4090-4096.
[112] Kayashita J, Shimaoka I, Nakajoh M, Yamazaki M and Kato N, The Journal of Nutrition, 1997; 127(7): 1395-1400.
[113] Repo-Carrasco R, Espinoza C and Jacobsen SE, Food Reviews International, 2003; 19(1-2): 179-189.
[114] Sabir SM, Mubbasher S, Hayat I and Gardezi SDA, Pakistan Journal of Nutrition, 2003; 2(3): 178-181.
[115] Goodnight Jr SH, Harris WS, Connor WE and Illlngworth DR, Arteriosclerosis, 1982; 2(2): 87-113.
[116] Reppas A, Swidan SZ, Tobey SW, Turowski M and Dressman JB, European Journal of Clinical Nutrition, 2009; 63(1): 71-77.
[117] Jenkins DJ, Josse AR, Wong JM, Nguyen TH and Kendall CW, Current Atherosclerosis Reports, 2007; 9(6): 501-507.

[118] Skolness SY, Durhan EJ, Jensen KM, Kahl MD, Makynen EA, Villeneuve DL and Ankley GT, Environmental Toxicology and Chemistry, 2012; 31(11): 2615-2624.
[119] Chen L, McNulty J, Anderson D, Liu Y, Nystrom C, Bullard S, Collins J, Handlon AL, Klein A, Grimes A, Murray D, Brown R, Krull D, Benson B, Kleymenova E, Remlinger K, Young A and Yao X, The Journal of Pharmacology and Experimental Therapeutics, 2010; 334(1): 164-170.
[120] Holme, Boman K, Brudi P, Egstrup K,Gohlke-Baerwolf C, Kesäniemi YA, Malbecq W, Rossebø AB, Wachtell K, Willenheimer R and Pedersen TR, The American Journal of Cardiology, 2010; 105(12): 1802-1808.
[121] Corey DR, “Protein engineering: principles and practice”, Eds. Jeffrey L. Cleland, and Charles S. Craik. New York: Wiley-Liss, 1996.