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A REVIEW: CHOLESTEROL AND ITS MANAGEMENT

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ABSTRACT
The most important sterol is cholesterol, which is produced by most human cells, mostly in the liver. It is a crucial component of cell membrane and acts as a precursor for the synthesis of bile acids, vitamin D, and steroid hormones. In essence, the body overregulates the homeostasis of cholesterol.This review delves into the origins of cholesterol, its biological functions, its structural description, its biosynthesis, and its byproducts, which include steroid hormone, bile salts, and acid. It also looks at the latest advancements in cholesterol management against cardiovascular disease risk factors, including cardiovascular disease, stroke, and atherosclerosis. Pharmaceutical and non-pharmaceutical drugs, botanicals, dietary changes, and exercise are all part of the current therapeutic arsenal for the treatment and prevention of cardiovascular disease.

KEYWORDS:Heart-related disease, LDL, HDL, ASCVD, NADPH, ATP

INTRODUCTION
Starting with the production of cholesterol, a structural element of cell membranes, several steroid hormones, vitamin D, and bile acids are produced. Cholesterol is necessary for regulating how cells function in addition to their structural role, which gives stability and mobility.[1,2]A hydroxyl group, a core sterol nucleus composed of four hydrocarbon rings, and a hydrocarbon tail make up the distinctive structure of the 27-carbon molecule known as cholesterol. Each and every steroid hormone has a core sterol nucleus, also known as a ring.[4, 5].Water cannot combine with the non-polar hydrocarbon tail or the core ring. As a result, apoproteins, a type of protein, and cholesterol combine to produce lipoproteins, which are subsequently carried by the bloodstream.[6]

Cholesterol is a structural element needed by all mammalian cell membranes. [7–8] While there was a time when eating a lot of Heart disease (CVD) was thought to be associated with elevated cholesterol levels. New study shows that this is not the case and that blood levels of LDL-C do not increase significantly. However, the results are still debatable, maybedue to the correlation with the intake of saturated fat. [9, 10, 11].Inspired by these novel discoveries and the understanding that cholesterol is essential for many essential physiological processes, the special Nutrients issue on "Cholesterol and Health" focuses on the roles of cholesterol and the impact of dietary cholesterol on several metabolic processes.[12,13,14]Research is now being done on the

body's diurnal cycle for manufacturing bile acids and cholesterol, as well as how the circadian clock influences cholesterol homeostasis. Developing targeted therapeutics to enhance metabolic health requires a fuller understanding of this system before examining the role of dietary cholesterol or the body's cholesterol as a risk factor for specific diseases, the main one being cardiovascular disease. This special edition of Nutrients contains a review of the research on the diurnal cycles of indicators for bile acid synthesis, absorption, and cholesterol formation. The bile acid and cholesterol synthesis cycles daily, however the study did not find any evidence of a diurnal pattern of cholesterol absorption. [15]

Animal cells are primarily composed of the sterol known as cholesterol. An adult man weighing 70 kg is said to have a value of 140g (2g/kg body weight). Because it has both hydrophilic and hydrophobic ends with its structure, the total lipid, which only makes up a small part of cholesterol, is amphipathic. The liver is essential to the upkeep and regulation of cholesterol homeostasis in living organisms.[16, 17, 18]By transforming cholesterol into bile salts, bile acids, and the unprocessed (free) form of cholesterol in bile, which is subsequently absorbed by the intestine, the liver removes cholesterol from the body. An imbalance between the amount of cholesterol entering and leaving human tissues leads to a build-up of cholesterol, which can cause health hazards such atherosclerosis (the production of plaque from fat deposits in blood arteries, which narrows blood channels) and later coronary heart disease.[19,20].

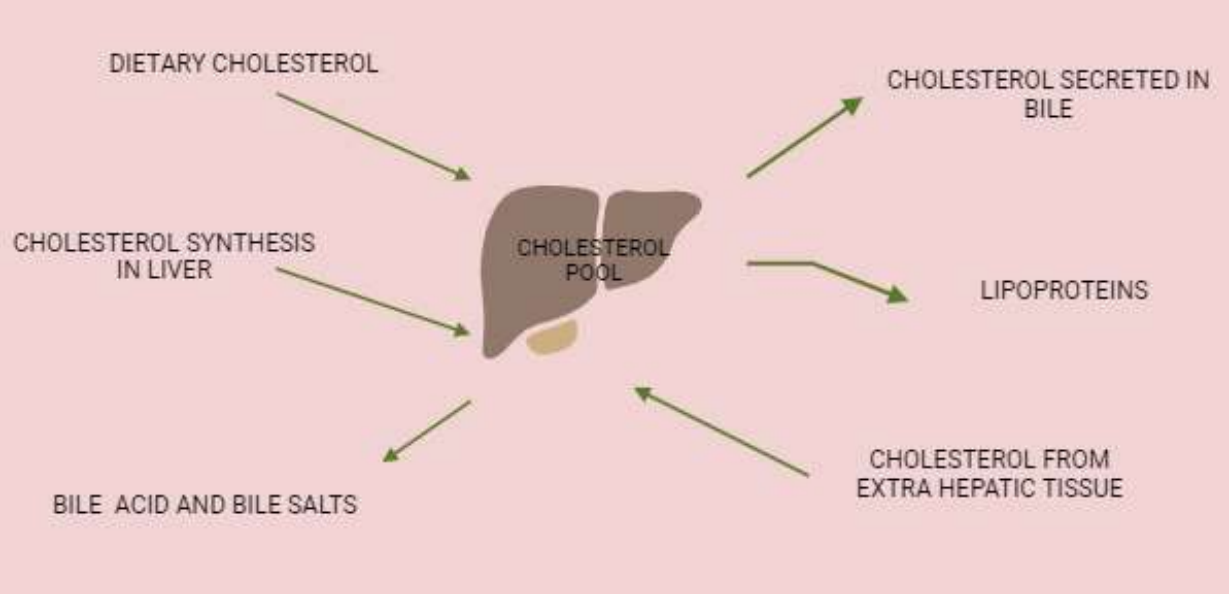

FIGURE 1: LIVER CHOLESTEROLRESOURCES

While many important cell processes depend on cholesterol, if abnormal blood concentrations are permitted to develop, cholesterol can be harmful to the body. It's interesting to note that early atherosclerotic cardiovascular diseases (ASCVD) are more likely to occur when LDL-cholesterol levels are excessive, a condition known as hypercholesterolemia.[21,22,23Patients must be adequately educated about the dangers of high blood cholesterol as well as how to reduce their serum cholesterol levels. For patients, changing their lifestyle to include less trans fat and

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saturated fat in their diet, increasing fibre and total calories (if they are obese), giving up smoking, and exercising are often effective ways to lower cholesterol. When behavioral modifications are not successful, medications that lower cholesterol, such as statins, should be used.[21, 24, 25].

BIOLOGICAL FUNCTION OF CHOLESTEROL

Cholesterol's Biological Purposes Cholesterol is necessary for life and cannot be replaced because it is known to carry out a number of vital tasks that can be summed up as follows: [26]

Cell membrane's structure:The structure of the membrane of animal cells includes cholesterol. Cholesterol has an active role in the fluidity, synthesis, and maintenance of animal cell membranes at normal temperature ranges. When cholesterol interacts with the sphingomyelin and phosphatidylcholine complex, it helps to increase the flexibility of the membrane.

Precursor for Synthesis of steroid: Cholesterol is biosynthesized into steroid hormones (including cortisol, aldosterone, and adrenal hormones), sex hormones (oestrogen, progesterone, and testosterone), vitamin D, and bile salts.

Transport of Fatty Acids: Fatty acids are transported to the liver by cholesterolwhere they are converted to cholesteryl esters for oxidation. Within seven hours of consuming dietary cholesterol, lipoproteins' extracellular medium allows for the transportation of absorbed fat around the body's tissues. [27, 28, 29]

Lipid Transport: In essence, cholesterol facilitates simple lipid transport in the body as a part of lipoprotein structure. Signal transduction: Several studies have shown and reported thatwhen coated with phospholipids, cholesterol functions as an electrical insulator and contributes to the transmission of cell signals.

.**Digestion and Absorption of food**: Food digestion is significantly influenced by cholesterol. The bile salts and acids that the liver produces are known as bile fluids. Cholesterol breaks down lipids by solubilizing them in the gall bladder. This process guarantees that fat molecules and fat-soluble vitamins A, D, E, and K are absorbed as best they can in the intestine. [30,31]

STRUCTURAL DESCRIPTION OF CHOLESTEROL

The primary structural component of cholesterol is a Trans ring made up of four hydrocarbons that are fused together to form the A, B, C, and D skeletons of steroid nuclei with branched hydrocarbon tails.The fused ring's carbons 18 and 19 have 2 methyl groups, the branched chain's carbons 21 and 27 have two methyl groups, and the carbons 5 and 6 have a double bond. In this structure, there are 46 hydrogen atoms, 1 oxygen atom, and a total of 27 carbon atoms. $C_{27}H_{45}OH$ is its chemical formula, and its molar mass is 386g/mole. Due to its tetracyclic cyclopenta [a] phenanthrene structure, cholesterol is known by its IUPAC-IUB nomenclature, cholest 18, 19, 21, and 27-tetra methyl-5-en-3-ol10.It is an amphipathic substance that contains both hydrophilic and hydrophobic components11.Cholesterol is a particularly important sterol in animals due to the location of the hydroxyl group (C-3), which defines it as an animal steroid. The structured arrangement of the OH group on the steroid nucleus (hydrocarbon head) and the

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branching hydrocarbon tail in cholesterol, therefore, causes animal sterols to absorb more quickly through the intestinal tract than plant sterols.[26,32]

BIOSYNTHESIS OF CHOLESTEROL

The body produces cholesterol in almost every tissue, although the liver (nearly 50%), gut (15%), adrenal cortex, reproductive tissues, and skin account for a significant share of the body's overall cholesterol pool. The daily production of cholesterol by a healthy adult is approximately 1g. The reaction's energy source is ATP, while its reducing equivalent is given as NADPH. Carbohydrates get their carbon structure from acetyl CoA acetate. A mole of cholesterol can therefore be synthesized using 16 moles of NADPH, 18 moles of acetyl CoA and 36 mole of ATP. Despite the fact that the cytosol of the cell is where cholesterol is mainly produced, the smooth endoplasmic reticulum and the cytoplasm both contain the required enzymes. [33, 34,]

CHOLESTEROL BIOSYNTHESIS STAGES

For ease of understanding, the enzymatic reactionsand the procedures involved in the generation of cholesterol are easily separated into six phases.The synthesis of 3-hydroxy-3-methylglutaryl (HMG) CoA, or HMG CoA, is the. (2) Mevalonate synthesis (3) Formation of Isoprenoid units Step four include the synthesis of lanosterol, the conversion of cholesterol, and the generation of Squalene. The cholesterol biosynthesis enzyme pathway reaction.[35]

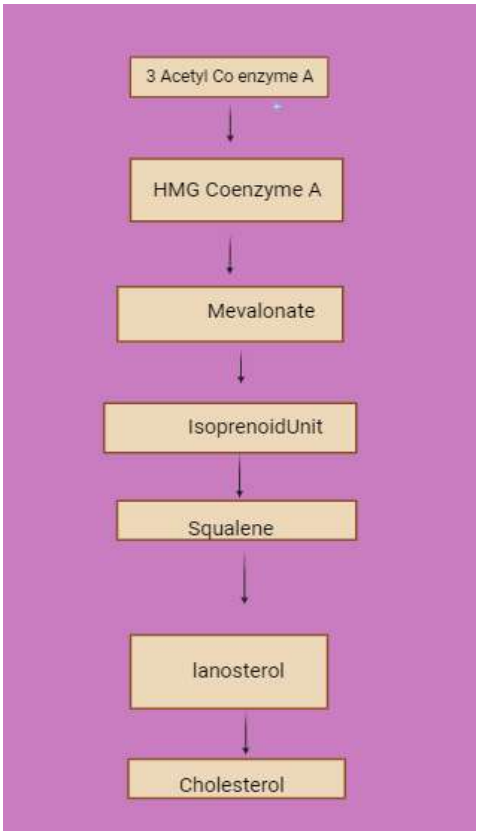

FIGURE 2:BIOSYNTHESIS OF CHOLESTEROL

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TYPES OF CHOLESTEROL

The different types of lipoproteins are as follow:

- **LDL (low density lipoprotein)** –The "bad" cholesterol is known as LDL. It carries cholesterol to different body cells from the liver. Given its greater serum level, there may be a higher chance of vascular diseases..
- **HDL (high density lipoprotein)** –It's known as "good cholesterol." HDL is said to protect against artery disease. It transports the fat from the cells back to the liver. Either the liver breaks it down or the body gets rid of it as waste.
- **Triglycerides (TG)**- This is the chemical form that most fat that humans eat comes in. Our bodies get TG from our external diet, or from a portion of it derived from other sources, such as carbohydrates. It is converted to TG and stored in fat cells by our bodies if we do not eat the diet that we adhere to. When we fast, TG is released from fat cells and consumed as a source of energy. This process is hormone-controlled..[36,37]
- **VLDL:**Chylomicrons outweigh triglycerides in the very low-density lipoproteins (VLDLs) secreted by the liver. To move cholesterol from the liver to the organs and tissues, the body needs very low density lipoprotein. Triglycerides with cholesterol combine to form their composition.[36,38, 39]

  The numerous forms of lipoproteins that circulate in the blood each serve a unique function. Lipoproteins are classified into four categories: high-density lipoproteins (HDL), intermediate-density lipoproteins (IDL), and very-low-density lipoproteins (VLDL). It is believed that LDL particles, which are important in the transport of cholesterol to peripheral tissues, contain at least two thirds of the circulating cholesterol. HDL molecules, on the other hand, are hypothesized to work the other way. They take the extra cholesterol and give it back to the liver so it may be eliminated. Clinically speaking, these two lipoproteins are important since they raise patients' risk for atherosclerotic vascular diseases: high LDL and low HDL. The essential roles of cholesterol within the cell are numerous. Cell membranes are connected to several of the main applications of cholesterol. It helps to maintain the membrane's fluidity and is necessary for its regular structure. The internal milieu of the cell can vary as a result of this fluidity's potential impact on some tiny molecules' capacity to diffuse through the membrane. The movement of materials inside cells is aided by cholesterol within the membrane. Cholesterol has a number of different biological purposes besides serving as a component of cell membranes.The fact that cholesterol is an essential precursor molecule for the synthesis of several other substances, such as bile salts, testosterone, aldosterone, progesterone, oestrogen, and vitamin D, is also notable.
  .[40]

DIGESTION, ABSORPTION AND UTILIATION OF CHOLESTEROL

A complex substance, cholesterol is eaten in food, broken down into simpler compounds by enzymes, absorbed by intestinal mucosal cells, then integrated and used by the body's cells. The

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entire breakdown of cholesterol in humans only converts about half of the cholesterol because the steroid ring structure is not broken down into CO2 and H2O. Before being removed from the body, cholesterol may be transformed by bacteria in the gut after being released into the bile and travelling there. The reduced derivatives of cholesterol, cholestanol, coprostanol, and vitamin D, are produced in this way to generate neutral faecal sterol.Yet the body excretes the integral ring nucleus of cholesterol as bile salts and bile acids in stool. [41]

ROLE OF CHOLESSTEROL IN VARIOUS DISEASAE

Table: 1 Cholesterol role in disease

SR.NO	**CHOLESTEROL INDUCED DISEASE**	**ROLE**	**REFERNCES**
1	Liver disorders may arise from the accumulation of excessive cholesterol in the liver.	Excess lipid accumulation in the cytoplasm of hepatocytes, disturbance of hepatic lipid metabolism, and liver inflammation and fibrosis (for NASH) are characteristics of common chronic liver disorders.	42, 43
2	B cell dysfunction may result from an excess of cholesterol accumulating in the pancreatic islets.	Abnormalities in insulin production and b cell death can result from cholesterol accumulation in pancreatic b cells. It was demonstrated that B cell lines, bTC3, and INS-1 cells were subjected to elevated cholesterol. It also changes the function membrane and enlarges insulin granules.	44
3	Pituitary-thyroid axis dysfunction may be brought on by excessive cholesterol buildup.	Pituitary-thyroid axis dysfunction may be brought on by excessive cholesterol buildup. A well-established clinical finding is the connection between hypercholesterolemia and hypothyroidism (Shin and Osborne, 2003). The traditional explanation for hypothyroidism-induced	45

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		hypercholesterolemia is a decrease in LDLR expression brought on by a thyroxin or Triiodothyronine shortage.	
4	Excess cholesterol accumulation may induce osteoarthritis	Osteoarthritis may result from an excess of cholesterol buildup. Another risk factor for osteoarthritis may be high cholesterol. Numerous reports have indicated that patients with osteoarthritis have significant quantities of cholesterol and cholesterol crystals in their synovial fluid.	46
5	An excessive buildup of cholesterol in the brain could lead to Alzheimer's disease.	When compared to other tissues, the brain has a high concentration of cholesterol. There has been a strong 6correlation during the last 20 years b7etween cholesterol and Alzheimer's disease, with familial hypercholesterolemia having a markedly increased prevalence of cognitive impairment.	47, 48
6	Overaccumulation of cholesterol may cause immunological malfunction.	The immune system is also impacted by high cholesterol. Mice lacking in Abca1/g1 experience symptoms of systemic lupus erythematosus.In that identical work, researchers found that Abca1/g1deficient dendritic cells exhibited elevated intracellular cholesterol accumulation, which was connected to elevated pro-inflammatory cytokine production and inflammasome activation. .	49
7	Severe COVID-19 infection may be more common in people who have high cholesterol.	Excess cholesterol accumulation may increase the incidence of severe COVID-19 A number of studies have shown associations between ele6vated cholesterol levels and	50

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		bacterial or viral infections, but the role of cholesterol in infection is still a matter of controversy. Membrane fusion is a key step for the entry of the SARSCoV-2 virus.	

MANAGEMENT OF CHOLESTEROL

A person's risk of heart attack, stroke, chest discomfort can all be significantly elevated by excessive cholesterol.Thankfully, there are several efficient therapy methods accessible. The emphasis in the revised recommendations is more on low density lipoprotein (LDL) cholesterol than on total cholesterol, which was the primary focus previously. Increased levels of low-density lipoprotein (LDL) are associated with an high risk of death, myocardial infarction, stroke, and required for coronary stenting or bypass surgery. Lowering LDL cholesterol has been linked to lower incidence of major cardiac events, according to studies conducted over the past 50 years. An elevated risk has also been associated with triglycerides, another kind of cholesterol. Conversely, research suggests that lowering high-density lipoprotein (HDL) cholesterol is not likely to increase risk, while raising HDL is associated with a reduced risk. It is nearly always possible to reduce cholesterol levels, especially LDL cholesterol and triglycerides, with medication in addition to weight loss (achieved by diet and exercise). Lipid levels with dietary changes, medicine, or a combination of the two.

Occasionally, a doctor will suggest trying specific lifestyle modifications before prescribing a medication. The optimal course of action for you will depend on your particular circumstances, which include your cholesterol levels, health issues, risk factors, food preferences, and way of life. Lifestyle modifications — If your low-density lipoprotein (LDL) cholesterol is high, you should attempt to alter certain parts of your daily schedule, like cutting back on total and saturated fat, losing weight (if you are overweight or obese), doing frequent aerobic exercise, and maintaining a nutritious diet high in vegetables and fruits.

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Using a plant-based diet as a strategy can reduce LDL cholesterol 21. Within six to twelve months, the advantages of these lifestyle adjustments typically start to show. However, there are wide variations in the effectiveness of changing one's lifestyle to lower cholesterol; therefore doctors may suggest beginning medication earlier. Medication – There are numerous drugs that can help lower increased LDL cholesterol levels. How each class of drug functions, how well it works, and how much it costs vary, your doctor will recommend a medication or medication combination for you based on your blood lipid levels and other individual factors.[51,52]

Flavones included in soy protein work similarly to oestrogen in the body. Eating a diet high in soy protein can raise levels of the good cholesterol (HDL) and slightly lower levels of triglycerides, LDL cholesterol, and total cholesterol. To lower cholesterol levels, however, regular protein shouldn't be substituted with supplements containing soy protein or isoflavones.It is anticipated that soy products and foods will improve lipid profiles and cardiovascular health

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because they are high in unsaturated fats and low in saturated fats. Tofu, soy butter, and several kinds of soy burgers are a few examples of soya goods.

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Garlic –Garlic may reduce cholesterol, although this is not proven. Green plant sterols and stanols — It is possible for plant sterols and stanols to prevent cholesterol from being absorbed through the intestines. Nuts, seeds, legumes, fruits, vegetables, and vegetable oils all naturally contain them. They can also be found in commercially produced foods like Benecol and Promise Active margarine, Minute Maid Premium Heart Wise orange juice, Rice Dream Heart Wise rice milk, and Benecol Soft Gels and Cholest-Off nutritional supplements. Although taking more plant stanols and sterols lowers cholesterol, there is no evidence that this lowers the risk of coronary heart disease.

Over time, supplements may increase danger. It is necessary to undertake more investigation before approving these products. LDL cholesterol can be lowered by reducing the amount of saturated fats, which are present in whole-fat dairy products, cheese, and red meats. You can also lower LDL cholesterol by exercising more and losing weight. The risk of coronary artery disease (CAD) has been discovered to be decreased by monounsaturated fats, which are present in olive oil, almonds, and fish fats. These fats also enhance HDL (high density lipoprotein) cholesterol and lower LDL cholesterol. Among the medications used to lower cholesterol include statins, bile acid resins, nicotinic acid, and fibrates. [53, 54]Herbs have been consumed for ages as food and for therapeutic purposes. Numerous herbs with hypolipidemic, ant platelet, antitumor, or immune-stimulating activities have attracted research attention as potential adjuncts to help lower the risk of cancer and cardiovascular disease. [55,56] Research is being done to identify herbal remedies with lipid-lowering properties. People who are at a higher risk of cardiovascular disease should engage in regular aerobic exercise and eat a plant-based diet high in fruits, vegetables, and legumes and low in saturated fat.[57,58]Additionally, there are a few herbs that can benefit those who have hyperlipidaemia, a disproportionate propensity to clot, poor blood flow, or other cardiovascular issues.[59, 60]

CONCLUSION

.Two new non-statin medications that have been shown in clinical trials to help lower high cholesterol have been approved by the FDA. Combining statins with nexletol and nexlizet can result in minimal or controlled adverse effects.Certain negative effects of the two new medications are not related to statins. According to the aforementioned study, having high cholesterol is a significant risk factor for heart disease.Dietary foods and new medications can help treat it. The consequences of cardiovascular disease pose a major threat to public health.These include the use of plants, herbs, dietary, exercise, foods therapies. Since dietary and de novo (endogenous tissue synthesis) sources both contribute to the excess cholesterol in the blood that causes hypercholesterolemia, it is important to limit your intake of dietary sources of cholesterol. You may also want to consider supplementing your diet with frequent exercise. If nutrition and exercise are maintained with attention, the risk of CVD and many other diseases

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may be decreased.The evidence that eating cholesterol increases the risk of heart disease in healthy individuals is not supported by the current body of data. However, there is an abundance of evidence indicating that trans fats and saturated fats increase the risk of heart disease. The fact that dietary cholesterol is often associated with diets high in saturated fatty acids may have contributed to the notion that it is atherogenic. Conversely, eggs are less costly, nutrient-dense, low in saturated fat, and abundant in protein and minerals. Nutrient-dense, calorie-controlled meals with balanced nutrients can be a part of the healthy eating pattern, as can a variety of vividly colored fruits and vegetables.

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