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High Cholesterol Disorders, Myocardial Infarction and Its Therapeutics

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Abstract

The current review article discusses several conditions linked to high cholesterol, including their causes, diagnoses, and treatments. Cardiovascular disease is one of the leading causes of death worldwide, and hypercholesterolemia is a standalone risk factor for the condition. Numerous cardiovascular illnesses (CVDs) and disorders, including myocardial infarction, hypertension, peripheral vascular diseases, and coronary heart diseases, were highlighted in this article. Low density lipoprotein (LDL) is the key factor in the majority of CVDs. It adheres to fatty deposits and forms plaques inside artery lumen, preventing the heart and other body organs from receiving enough blood and oxygen. Cardiomyopathies and dyslipidemias are the most common causes of morbidity and mortality in men and place a considerable health cost on society. Age, hypertension, obesity-induced blood pressure, and a rise in plasma cholesterol are all factors that raise the risk of coronary heart disease (CHD). Calorie intake must be controlled, meal composition must be changed, a natural cycle must be established, and circadian timeliness must be maintained in order to live a healthy life. To lower the risks of metabolic and cardiovascular diseases, try to go vegetarian and always consume traditional plant-based diets and herbal remedies. Exercise yoga and aerobics every day to stay physically healthy, and have your blood pressure, blood sugar, and cholesterol levels checked on a regular basis. Follow your family doctor's recommendations for managing high cholesterol risks and diagnosing CVD, obtain a lipid profile, take the recommended medications, maintain composure, and adopt a positive outlook for a long and healthy life.

Keywords

Hypercholestemia, Coronary Heart Diseases (CHD), Cardiovascular Diseases. Hypercholestemia, Cardiomyopathy, Cardiac Infarction, Risks, Diagnosis, Lipoproteins, Lipid Profile Polyunsaturated Fatty Acids, Antioxidants

1. Introduction

Increased blood lipid (fat) levels are what cause high cholesterol. Hyperlipidemia and hypercholesterolemia are other names for it. Inactivity and a high diet of animal fats are the two main causes of hypercholestemia. There are two essential classifications of cholesterol: "bad cholesterol" and "good cholesterol" (Table 1 & Table 2). Extra cholesterol is provided by dietary animal fats, and consumption of these fats has a big impact on total cholesterol levels. Low-density lipoprotein (LDL) is related to high levels of bad cholesterol. This causes fatty deposits or plaques to accumulate in arteries, which in turn causes the lumen to become clogged or narrowed and restricts blood flow. Blood flow across blood arteries is hampered by elevated cholesterol levels. According to Fancher *et al.* [1], if a

Table 1. Showing levels of blood cholesterol level and its harmful effects.

LDL (Bad) Cholesterol level	LDL Cholesterol category	Harmful effects	Remedy and therapeutics
70 mg/dL.	Low optimal*	Cardiovascular disorders	Use omega-3 fatty acids/fish oil and fibers
100 - 129 mg/dL	Near optimal**	Start of atherosclerosis	Use red yeast rice, garlic
130 - 159 mg/dL	Borderline high**	Initiation of plaque formation, chest pain (angina) and heart attack	Sustained-release by niacin, "no-flush" niacin and niacinamide
160 - 189 mg/dL	High**	Risk of heart diseases and stroke.	Use of anti-oxidants, yoga and exercise
190 mg/dL and above	Very High***	Severe cardiac infarction and brain stroke,	Surgery, statin therapy and intensive care

Supplemental fiber diet cut down LDL by 5% to 15%. *An unhealthy diet and eating high levels of saturated fat. **Acrolein, found in cigarettes, stops HDL transporting cholesterol from fatty deposits to the liver, leading to narrowing of the arteries (atherosclerosis), hence avoid smoking. ***High diabetes or high blood pressure (hypertension).

Table 2. (a) Showing levels of blood HDL cholesterol and total cholesterol level with their clinical categories; (b) Showing daily calorie requirements based on supply of fats.

(a)

HDL good cholesterol	Effect category	Total cholesterol levels	Category
Less than 40 mg/dL	Major risk factor for developing heart disease	Less than 200 mg/dL	Desirable
60 mg/dL	Optimal to reduce risk for heart disease	200 - 239 mg/dL	Borderline high
70 mg/dL	Fatal	240 mg/dL	High
80 mg/dL	Fatal	More than 240 mg/dL	Extremely high

*Use healthy diet having high levels of polyunsaturated fatty acids.

(b)

Calories per day	Total fat	Saturated fat
1500	42 - 58 grams	10 grams
2000	56 - 78 grams	13 grams
2500	69 - 97 grams	17 grams

*Source: U.S. National Library of Medicine.

plaque ruptures, a blood clot restricts blood flow within the lungs.

This is extremely toxic and causes atherosclerosis when it combines with other elements (fatty deposits) to form plaques in the arteries (Figure 1). These plaques persist inside arteries for years and enlarge over time. These can occasionally fracture suddenly, restrict the flow of blood inside the lungs, and be extremely lethal. Blood flow is restricted by high cholesterol, which raises the chance of a heart attack or stroke [2]. High cholesterol causes internal inflammatory diseases like lupus and is directly related to many other health issues like coronary artery disease. According to Hosseini *et al.* [3], this excessive cholesterol buildup is influenced by food, age, sex, and a family history of heart disease. High-density lipoprotein (HDL), also known as "good cholesterol", has a lower concentration of cholesterol. High-density lipoproteins (HDLs) transport cholesterol to the liver and regulate cholesterol levels (Table 3 & Table 4). The liver produces enough cholesterol to meet the body's needs and eliminates the remaining cholesterol. Untreated, high cholesterol can also lead to high blood pressure (Figure 2).

There are two major causes of cardiovascular diseases and disorders. The first is the metabolic storage of the excess adipose tissue in the body after dietary use. The second cause is genetic or hereditary disorders. Excess lipids in the blood stream are the primary cause of the generation of cardiovascular diseases, particularly myocardial Infarction and Stroke. Furthermore, lethargy and inactivity,

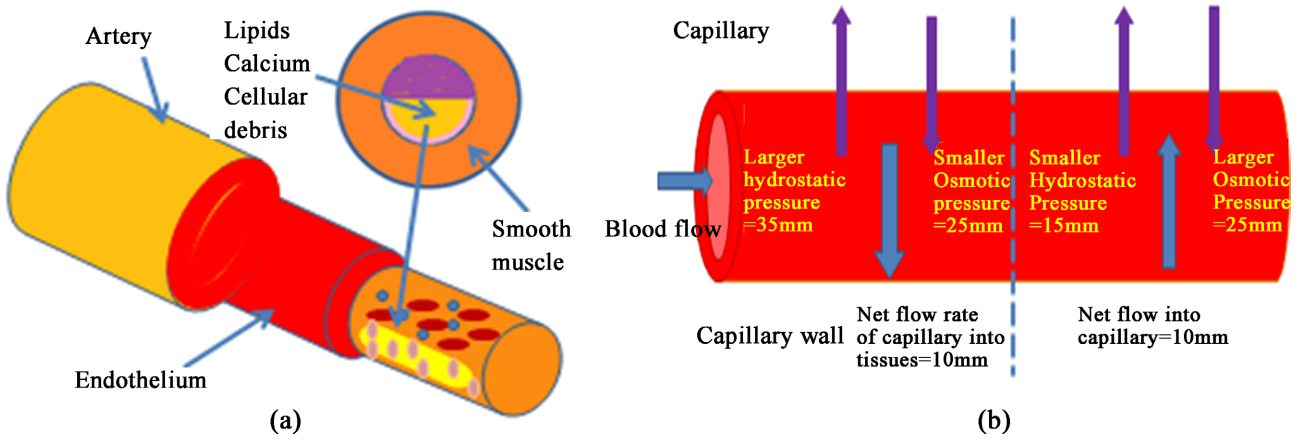

Figure 1. Showing blood flow inside capillaries and pressure exerted on its wall.

Table 3. Showing levels of blood triglyceride level with remedy and therapeutics.

Triglycerides	Effect category	Reason	Remedy and therapeutics
<150 mg/dl	Desirable	Normal body activity	Use of fruits and vegetables
150 - 199 mg/dl	Border line	Obesity, over eating and fat rich diet	Avoid sugar and refined carbohydrates, control body weight.
200 - 499 mg/dl	High risk	Type 2 diabetes, hypothyroidism, and chronic kidney disease	Avoid alcoholic drink, and smoking

*Use of docosahexaenoic acid (DHA) and eicosatetraenoic acid (EPA), and a short-chain fatty acid known as alpha-linolenic acid.

Table 4. Various classes of lipopoteins with their density, size and their structural lipids.

Lipoprotein	Density	Size	Major lipids	Major apo-proteins
Chylomicrons	<0.930	75 - 1200	Triglycerides	apoB-48, apoC, apoE, apoA-I, A-II, A-IV
Chylomicron Remnants	0.930 - 1.006	30 - 80	Triglycerides Cholesterol	apoB-48, apoE
Chylomicron Remnants	0.930 - 1.006	30 - 80	Triglycerides Cholesterol	apoB-48, apoE
VLDL	0.930 - 1.006	30 - 80	Triglycerides	apoB-100, apoE, apoC
IDL	1.006 - 1.019	25 - 35	Triglycerides Cholesterol	apoB-100, apoE, apoC
LDL	1.019 - 1.063	18 - 25	Cholesterol	apoB-100
HDL	1.063 - 1.210	5 - 12	Cholesterol Phospholipids	apoA-I, apoA-II, apoC, apoE
Lp (a)	1.055 - 1.085	~30	Cholesterol	apoB-100, apo (a)

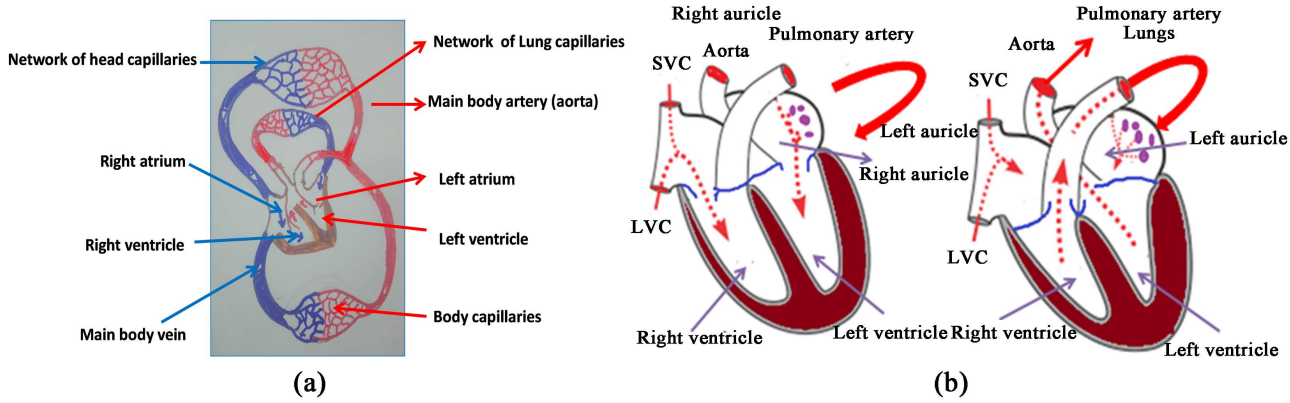

Figure 2. Showing systemic and pulmonary circulation and maintenance of cardiac flow.

poor dietary habits, alcohol and tobacco consumption are on the rise and are causing global cardiac health issues. These are the main causes of the large number of deaths worldwide [4]. Nowadays, the majority of the people suffer from obesity-induced cardiovascular diseases, such as high blood pressure, inflammation of the blood vessels, blood vessel atrophy and type 2 diabetes. Familial hypercholesterolemia is an inherited condition characterized by very high levels of cholesterol in the blood. This hereditary condition, which is primarily a monogenic illness, is brought on by a chromosome 19 abnormality. Due to its impact on plasma cholesterol levels, it poses an elevated risk of early atherosclerosis and accompanying cardiovascular consequences. Since it has to do with the accumulation of too much cholesterol in tissues other than the heart and blood vessels, it is one of the primary causes of cardiovascular illnesses. Tendon xanthomas are distinctive growths that develop when cholesterol builds up in the tissues that connect muscles to bones (tendons). These growths most often affect the Achilles tendons, which attach the calf muscles to the heels, and tendons in the hands and fingers. Xanthelasmata, or yellowish cholesterol deposits, can form beneath the skin of the eyelids.

Mutations or variations in the LDL-R, APOB, and PCSK9 genes are the pri-

mary causes of familial hypercholesterolemia (FH). These genes are in charge of controlling cholesterol levels and removing excess cholesterol from your blood. Because of mutations in one of these three genes, between 60 and 80 percent of persons have FH. LDL cholesterol, often known as bad cholesterol, cannot be eliminated from the body as a result of the abnormality. LDL levels in the blood rise as a result of this. Patients with FH are still more likely to develop heart disease and have an early heart attack. When professional assistance is unavailable and signs of hereditary FH start in childhood, the patient dies before age 20.

It increases a number of cardiovascular disease risks, including: diabetic cardiomyopathy (DCM), obesity-induced blood pressure, blood vessel inflammation, and arteriosclerosis. Reactive oxygen species (ROS) are released in excess, which promotes lipid peroxidation [5]. Another factor that contributes to hypercholesterolemia is obesity, which also involves oxidative stress, adipose tissue malfunction, and hormone dysregulation. De novo lipogenesis in intra-abdominal organs is also increased. Through risk factors such raised fasting plasma triglycerides, high LDL cholesterol, low HDL cholesterol, elevated blood glucose and insulin levels, and high blood pressure, obesity raises the risk of cardiovascular disease. Alternately, polygenic FH—which is the aggregation of common cholesterol-increasing alleles—can provide the classic clinical presentation of FH. Risk factors from the environment and genetics both contribute to familial hypercholesterolemia. The quantity of cholesterol in the blood and the risk of coronary artery disease are significantly influenced by lifestyle factors such as food, exercise, and smoking. In addition, a person's sex, age, and chronic illnesses like diabetes and obesity have an influence on the condition's prognosis. LDL cholesterol levels may rise as a result of several drugs. Beta-blockers, thiazide diuretics, certain forms of birth control, antiviral medications, anticonvulsants, retinoids and corticosteroids, and growth hormones are a few of them.

It also exacerbates atherosclerosis and oxidative stress in patients [6], causes bioenergetic disturbances and disrupts cardiac function [7]. Alterations in cardiac energy metabolism play an important role in the development of diabetic cardiomyopathy. This is a severe pathological condition associated with perturbed lipid levels and physiological redox homeostasis. However, diabetes, hypertension, hypertension and hypercholesterolemia increase the risk of cardiovascular disease (CVD) and cause high mortality in the human population [8]. This article points out potential risks of high cholesterol, its side effects, morbidity, regulation of cholesterol levels and its treatment.

Source of information

For writing this comprehensive research review on "high cholesterol related disorders" various databases were searched. For collection of relevant information specific terms such as medical subject headings (MeSH) and key text words, such as high cholesterol related disorders, risks and therapeutics published till 2023 were used in MEDLINE. High cholesterol related disorders are cause of CVDs and CHDs. *Most specially* for retrieving all articles pertaining to the Rea-

sons and pathological effects of hypercholestemia and its therapeutics, electronic bibliographic databases were searched and abstracts of published studies with relevant information on the hypercholestemia were collected. Furthermore, additional references were included through searching the references cited by the studies done on the present topic. Relevant terms were used individually and in combination to ensure an extensive literature search. For updating the information about *a subject* and incorporation of recent knowledge, relevant research articles, books, conferences proceedings' and public health organization survey reports were selected and collated based on the broader objective of the review. The present review aimed to systematically analyze published data on the hypercholestemia, reasons, risks and pathological effects. This was achieved by searching databases, including SCOPUS, Web of Science, and *EMBASE*, Pubmed, Swissprot, Google searches and Cochrane library were searched. From this common methodology, discoveries and findings were identified and summarized in this final review.

1.1. What Is High Cholesterol?

Cholesterol (also called polyols) is a lipid that is waxy and fat-like. It can be found in foods like egg yolk, meat and poultry, fish and milk. Cholesterol plays an important role in cell membranes and in the production of steroid hormones. Some of these lipids are produced in the body. Total cholesterol is the sum of the cholesterol of the three lipoprotein fractions. 50% of serum cholesterol is in LDL, which is also dominated by cholesterol content, and in VLDL is dominated by triglyceride content. Plasma cholesterol is determined by the amount of food ingested, the amount synthesized in the body, the rate of catabolism, and biliary excretion. The body synthesizes most of the cholesterol it needs and gets the rest from food. Since cholesterol is largely insoluble in blood, it is packaged with proteins and phospholipids to form lipoprotein complexes and circulates in the bloodstream. It also depends on the intestinal reabsorption of bile acids and plasma tissue balance. Cholesterol is transported in plasma lipoproteins. They are divided into four major classes: high density lipoproteins (HDL-C), low density lipoproteins (LDL-C), very low density lipoproteins (VLDL-C), and chylomicrons. Dietary unsaturated fatty acids with two or more double bonds have been shown to affect plasma cholesterol. The mechanism by which polyunsaturated fatty acids lower serum cholesterol is unclear, but it involves a reduction in VLDL synthesis (**Tables 1-3**).

It is frequently hypothesized that a low HDL to LDL ratio promotes atherogenesis and, in turn, predisposes to CHD. Cholesterol is an essential component of cell membranes and steroid hormones. Cholesterol is found in all foods of animal origin. Some of these are synthesized in the body. Total cholesterol is the sum of cholesterol from the three lipoprotein fractions. 50% of serum cholesterol is in LDL, also dominated by cholesterol content, and triglyceride content in VLDL. Plasma cholesterol is determined by the amount of food ingested, the

amount synthesized in the body, the rate of catabolism, and biliary excretion. The body synthesizes most of the cholesterol it needs and gets the rest from food. Since cholesterol is almost insoluble in the blood, it is packaged with proteins and phospholipids to form lipoprotein complexes and circulates in the bloodstream. It also depends on the balance between intestinal reabsorption of bile acids and plasma tissue. Cholesterol is transported in plasma lipoproteins. They are classified into four main classes.

High density lipoprotein (HDL-C), low density lipoprotein (LDL-C), very low density lipoprotein (VLDL-C), and chylomicrons. Unsaturated fatty acids with two or more double bonds have been shown to affect plasma cholesterol levels. The mechanism by which polyunsaturated fatty acids lower serum cholesterol levels is unknown, but involves a reduction in VLDL synthesis. It is hypothesized that a low HDL to LDL ratio promotes atherogenesis, resulting in CAD.

Cholesterol buildup in arteries causes many diseases. 95% of heart attacks are caused by coronary artery spasms, narrowing of blood vessels, trauma or rupture of coronary arteries, blood clots or air bubbles lodged in coronary arteries (emboli), electrolyte imbalances, nutritional and eating disorders, stress, atherosclerosis or cardiomyopathy, caused by congenital diseases. Heart defects can cause heart attacks (Figure 1 & Figure 2). Occasionally, plaque builds up in the coronary arteries (arteries of the heart) and ruptures or ruptures, and blood clots can become lodged in the ruptured areas. A clogged artery causes blood to flow out of the heart muscle and cause a heart attack.

1.2. Triglycerides

Fatty acids are the major building blocks of triglycerides and lipids. The maximum amount of stored triglyceride is derived from fatty acid constituents. The most significant characteristic of fatty acids is their hydrophobic nature to triglycerides and lipid substrates. Synthesis of triglyceride and lipid substrates is highly relevant for membrane function. Cholesterol is a precursor of steroid hormones and bile acids. Sex hormones and adrenal cortex hormones are also precursors of cholesterol. In animals, biosynthesis of triglycerides is a highly active metabolic process because of its energy requirements.

Triglycerides are a type of lipid (fat) present in the blood. As cholesterol levels increase, triglyceride levels in the blood also increase significantly. Moreover, there is a good correlation between TG and CHD, as well as between total serum cholesterol and CHD. High triglyceride levels are also known as hyper-triglyceridemia (Table 3). Although it has no symptoms, it indicates an underlying problem and is a risk factor for several health conditions. There are many reasons for increased triglycerides in the blood, including: Inactivity, high dietary fat and sugar intake, alcohol consumption, smoking, and obesity. High triglyceride levels can also increase the risk of other organ problems, such as fat accumulation in the liver and pancreas. These increase the risk of heart disease, stroke and pancreatitis. To reduce triglyceride levels, eat fruits, vegetables and whole grains and

avoid added sugars, fats and hot drinks [9]. Other unaffected causes include menopause and chronic conditions such as thyroid, kidney and liver disease.

1.3. Lipoproteins

Largest lipid-rich lipoprotein involved in the distribution of triglycerides from food to cells through the bloodstream. Very low density lipoproteins (VLDL) retain endogenously organized triglycerides [10]. Low density lipoprotein (LDL) delivers cholesterol to peripheral cells. It persists and deposits in the arterial lumen, causing atherosclerosis. This increase in plasma lipid levels is responsible for most cardiovascular diseases [11]. However, try to eat a healthy diet rich in whole grains, fruits and vegetables to reduce your risk of cardiovascular disease. Play sports regularly. Lose weight. No Smoking. Reduce stress and use antihypertensive drugs to prevent heart attacks and strokes caused by atherosclerosis. The high density lipoprotein (HDL) gathers the excess cholesterol for transport back to the liver [12] (**Table 4** & **Table 5**).

A lipid profile is a clinical test that includes four basic parameters, *i.e.*, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides [13]. This test, alone or in combination with other tests, is considered a biomarker for predicting cardiovascular risk for cardiovascular risk assessment [14]. Lipid profiles of fasting blood samples should not be performed because non-sober samples have certain limitations. Herbal regimens and a favorable dietary structure can be followed to treat cardiovascular disease [15]. Cholesterol deposition carried by low-density lipoproteins causes devastating brain changes induced by hypercholesterolemia [16]. Familial hypercholesterolemia (FH) is an inherited disorder characterized by abnormally elevated serum LDL (low-density lipoprotein) cholesterol levels from birth, leading to premature atherosclerotic cardiovascular disease [17] (**Figure 1(a)** & **Figure 1(b)**). Therefore, for timely treatment, lipid profiling is highly essential to know the serum concentrations of total cholesterol, LDL-C, HDL-C, triglycerides, apoA and apoB, SGOT, SGPT, glucose and insulin in the blood and plasma [18] (**Table 4** & **Table 5**).

Table 5. Showing lipoprotein related disorders and its pathological effects found in humans.

Type of defect	Lipoprotein increased	Pathological effects
Familial hypercholestemia	LDL	Defective or lack of LDL receptors
Familial defective apoB	LDL	apoB with LDL receptor binding
Familial combined hyperlipoproteinemia	VLDL and LDL	Overproduction of apoB containing lipoproteins
Dysbetalipoproteinemia	Remnants	Abnormal apoE
Hypertriglyceridemia	Moderate-VLDL, Severe VLDL and Chylomicrons	Over production of triglyceride; defective catabolism
Genetic lipoprotein lipase or apo CII deficiency	Chylomicrons	Defective catabolism

2. High Cholesterol Induced Morbidities

2.1. Coronary Heart Disease (CHD)

Coronary heart disease evokes when heart's blood supply is blocked or interrupted by a build-up of fatty substances in the coronary arteries. According to the Centers for Disease Control and Prevention (CDC), coronary artery disease (CAD) is the most common form of heart disease, killing about 370,000 people in the United States each year. Plasma cholesterol is very important in the development of CHD. The risk of CHD appears to increase with increasing plasma cholesterol concentrations. CHD occurs when atherosclerosis causes plaque to build up in the arteries that supply oxygenated blood to the heart. The buildup of plaques in coronary arteries causes a form of chest pain called angina and greatly increases a person's risk of having a heart attack. Patients of familial hypercholesterolemia face risk of coronary artery disease at a young age. When excess of cholesterol get deposited on the inner walls of blood vessels, particularly the arteries that supply blood to the heart (coronary arteries). The abnormal buildup of cholesterol forms clumps (plaques) that narrow and harden artery walls. As the plaques get bigger, they can clog the coronary arteries and restrict the flow of blood to heart and various body organs. It suddenly evokes chest pain (angina pectoris), heart attack, heart failure, or an irregular heartbeat called an arrhythmia.

Coronary artery disease is a common heart condition. This disease occurs when the major blood vessels supplying your heart (the coronary arteries) are unable to deliver enough blood, oxygen, and nutrients to your heart muscle. The main causes of coronary artery disease are cholesterol buildup (plaque) in the coronary arteries and inflammation. Coronary Arthritis signs and symptoms occur when your heart is deprived of oxygen-rich blood. Carotid artery disease affects the two large arteries in the neck that supply blood to the brain. Carotid artery disease, often associated with atherosclerosis, occurs when arteries become narrowed by plaque buildup (**Figure 1(a)** & **Figure 1(b)**). If the carotid artery's blood supply is disrupted, the risk of stroke increases (**Table 5** & **Table 6**).

As bad cholesterol is due to presence of larger fractions of low-density lipoproteins (LDLs) in streaming blood, these proteins transport cholesterol from its site of synthesis in the liver to the various tissues and body cells, where it is separated from the lipoprotein and is used by the cell.

LDL is the major carrier (about 67%) of serum cholesterol. LDL delivers cholesterol to tissues of need (adrenal gland, gonads, etc.) all of which have LDL receptors on the plasma membranes that detect apoB-100. LDL contains mostly cholesteryl ester and aprob-100. LDL has a density (1.019 - 1.063 g/ml) of 20% - 50% protein and 50% - 50% cholesterol (CE/FC). When there is an excess of fatty acids and cholesterol in the liver, these are converted into triacyl-glycerols (TCGs) and packaged with apo-proteins into LDL. Excess carbohydrates may also be converted to TCGs and transported as LDL. VLDL contains apoBs

(apoB-100), (apoC-I), and (apoE). VLDL is distributed via capillaries from the liver to tissues. In tissues, LPL (lipoprotein lipase) activated by apoB-II catalyses the release of the free fatty acids present in VLDL, similar to how chylomicrons (apoE) inhibit LPL.

Free fatty acids are absorbed into the adipose tissue, where they are stored as triglycerides. After partial removal of triglycerides, triglyceride VLDL remains (IDL). Further removal of triglycerides produces LDL, which is the result of the metabolism of triglycerides VLDL. Cholesterol esters (Ce) and triglycerides (TG) cannot be dissolved in water (Plasma). As a result, they are packaged lipoprotein (Lipoprotein) consisting of an inner core composed of Ce and TG with an outer coat of apoietin, FC, and Phospholipid. Lipoprotein transport to various tissues is possible.

A heart-healthy diet (low in saturated fat and sodium) and regular exercise are very important in reducing the risk of coronary artery disease. The disease is characterized by hypertension, high LDL (bad) cholesterol, low HDL (good) cholesterol, or diabetes [19]. The main causes of coronary artery disease are smoking, high-fat diet, diabetes, high cholesterol, hypertension, and obesity. Drugs that block newly synthesized cholesterol are used to rapidly regulate cholesterol levels and reduce dietary cholesterol intake. Of course, HMG-CoA reductase controls the rate of synthesis. Following a well-regulated diet lower the chances of development of heart diseases, especially coronary artery diseases, in many settings. All factors associated with CHD (e.g. plasma cholesterol, high blood pressure, smoking, physical inactivity). There is a dietary heart hypothesis that manifests in the form of elevated cholesterol and low-density lipoprotein (LDL) levels in the development of atherosclerosis (**Figure 1(a)** & **Figure 1(b)**) [19]. However, altering dietary fatty acid intake primarily promotes the use of dietary polyunsaturated fatty acids. Also, reducing saturated fat intake by less than 30% reduces the risk of CHD. A panel of W.H.O. experts has concluded that there is a triangle relationship between normal diet, blood cholesterol levels, and coronary artery disease (**Table 5** & **Table 6**).

Hypercholesterolemia is a lipid disorder in which your low-density lipoprotein (LDL), or bad cholesterol, is too high. This makes fat collect in arteries (atherosclerosis), which puts you at a higher risk of heart attack and stroke. High cholesterol and its deposition inside the lumen of arteries lead to the formation of plaques that restrict blood flow. This is one of the leading risk factors for cardiovascular disease and stroke. High blood pressure, high LDL cholesterol, diabetes, exposure to secondhand smoke, obesity, poor diet, physical activity, alcohol consumption and drugs are other traditional risk factors. Genetic risk factors include family history that strongly indicates very early symptoms of a heart disease or cardiovascular disease are hypoglycemia (high cholesterol), metabolic syndrome, chronic kidney disease, chronic inflammation conditions, early menopause, high risk ethnicity and exceeding triclyceride (T-acyl)-glycerol level of 175 mg/dL.

Table 6. Most common high cholesterol disorders identified in various human groups.

Name of disease	Reasons	Patho-physiological effects
Diseases associated with high cholesterol level		
Atherosclerosis	Buildup of fats, cholesterol and other substances in and on the artery walls	Cause arteries to narrow, blocking blood flow. The plaque can also burst, leading to a blood clot.
Stroke	Blocks blood supply to part of the brain or when a blood vessel in the brain bursts.	Parts of the brain become damaged or die, paralysis or numbness of the face, arm or leg.
Cardiovascular disease	Disease of the heart or blood vessels	Coronary heart disease and heart attacks, blood clot (thrombosis) build-up of fatty deposits inside an artery
Xanthomas (familial hypercholesterolemia)	Autosomal dominant inherited genetic disorder, disturbance in lipoprotein metabolism	Persistent hypercholesterolemia
Tangier disease (familial HDL deficiency)	Inherited disorder characterized by significantly	Reduced levels of high-density lipoprotein (HDL) in the blood.
Diseases associated with low cholesterol level		
Huntington disease	Inherited disorder that causes nerve cells (neurons) in parts of the brain to gradually break down and die	Disease attacks areas of the brain that help to control voluntary (intentional) movement, as well as other areas
Trauma and hemorrhagic stroke	Blood vessel in the brain leaks or ruptures, bleeding disorders, or an aneurysm.	Contralateral hemispheric damage, traumatic brain injury
Neuropsychiatric disorders	Depression, suicide, anxiety, impulsivity, and aggression), schizophrenia (SZ), bipolar disorder (BD), major depressive disorder MDD)	Cognitive deficit disorders, behavioural disorders arise due to cerebral disturbance, seizures, attention deficit

2.2. Hepatic Inflammation and Fibrosis

Excess dietary cholesterol accumulates preferentially in the liver and promotes the development of nonalcoholic steatohepatitis (NASH), which is characterized by progressive liver inflammation and fibrosis. Understanding the regulatory effects of cholesterol on the transcriptome of innate immune cells may help identify new therapeutic targets for NASH intervention [20].

2.3. Diabetic Cardiomyopathy and Cardiovascular Diseases

Blood vessel problems develop slowly and do not cause symptoms, but can suddenly lead to life-threatening problems such as heart attacks and strokes. Arteries pump oxygen-rich blood from the heart to the rest of the body, and veins carry blood back to the lungs to supply oxygen. Both types of blood vessels are important for blood circulation in the body. If there is artifact or debris in the lumen of the artery, it can cause problems with blood circulation [21] (**Figure 1(a)** & **Figure 1(b)**).There is a risk of blood clots and thrombosis. Both pose more serious health risks that can affect your arteries and veins, such as blood clots, high cholesterol, and plaque buildup, and help to protect your health.

2.4. Atherosclerosis

Cardiovascular disease (CVD) and other related diseases, such as myocardial infarction, hypertension, peripheral vascular disease, coronary artery disease, cardiomyopathy and dyslipidemia, are a significant health burden and a major contributor to human morbidity and mortality [10]. Atherosclerosis is caused by deposition of lipoproteins and cholesterol in the lumen of arteries. Arteriosclerosis is a common condition that affects the flow of oxygen-rich blood to the body. The disease develops when plaque (cholesterol, fat, calcium) builds up in arteries, restricting blood flow (**Figure 1(a)** & **Figure 1(b)**). Eventually arteries become clogged, which can lead to serious problems such as heart attacks and strokes. High cholesterol, especially high blood LDL cholesterol and low blood HDL cholesterol, poses a significant risk of atherosclerosis [22] (**Table 5** & **Table 6**).

Particularly in vascular diseases such as atherosclerosis, atherogenic plaques result from the accumulation of lipid and fibrous elements in the subendothelial space of the aorta and subsequent formation of lesions within the coronary and cerebral arteries [11]. The etiology of atherosclerosis is multifactorial and many modifiable and unmodifiable risk factors have been identified [23]. Atherosclerosis is a chronic, multifactorial disease primarily characterized by altered blood lipid profiles and inflammation of the blood vessel walls. Lipid peroxides in low-density lipoproteins (LDL) are known to play an important role in arteriosclerosis and atherosclerosis [24]. Timely prevention and treatment of atherosclerosis is therefore of great importance to reduce the risk of developing its clinical manifestations [25]. These risk factors collectively contribute to the development, progression and rupture of atherosclerotic plaque [26] (**Table 5** & **Table 6**).

2.5. Peripheral Arterial Disease (PAD)

It is very similar to atherosclerosis and is more likely to occur with age. In peripheral arterial disease, arteries far from the heart (usually in the pelvis and legs) become artefacts and narrow due to plaque buildup. These interfere with the blood supply, causing severe pain and fatigue in the legs due to reduced blood flow to the muscles (**Figure 1(a)** & **Figure 1(b)**). It can also occur during training to climb stairs. Hypertension, high cholesterol, atherosclerosis, diabetes and smoking increase his risk of PAD [27]. To reduce your risk of PAD, exercise regularly to control your blood pressure and cholesterol levels. Eating a healthy diet and maintaining a healthy weight can reduce the risk of PAD. Varicose vein pain also interferes with blood circulation. Varicose veins form when blood collects in veins, usually due to problems with the one-way valves that return blood to the heart. If varicose veins are causing pain, swelling, burning, or itching, the medical problem should be treated. Avoiding prolonged standing and wearing compression stockings can reduce blood buildup and the risk of CVI.

2.6. Pulmonary Embolism

Pulmonary embolism (PE) is caused by smoking, use of estrogen hormone therapy, physical inactivity, and obesity. If a blood clot breaks and travels through the bloodstream to the lungs, this is a serious and fatal complication. The sudden interruption of blood flow to the pulmonary arteries damages the blood and reduces oxygen levels. It is also one of the important reasons for sudden death with warning signs such as chest pain and hemoptysis [28] (**Figure 2(a)** & **Figure 2(b)**).

2.7. Per-Cutaneous Coronary Intervention

Per-cutaneous coronary intervention (PCI) is used to restore blood flow in the affected myocardium (**Figure 2(a)** & **Figure 2(b)**). This involves inserting a catheter-based device into a large blood vessel, usually near your thigh or wrist. PCI is an important tool for restoring blood flow, and the earlier it is performed, the more likely it is to have a favorable outcome. Hospitals measure their ability to treat heart attacks using a metric called door-to-balloon time. This is the average time it takes people from first arriving at the emergency room to undergoing PCI. In PCI, a stent is often placed at the site of the blockage to keep the artery open to prevent new blockages from forming in the same place.

Coronary artery bypass graft surgery is used to treat people who have severely blocked coronary arteries and who may undergo coronary artery bypass graft surgery. This surgery is often called open heart surgery, bypass surgery, or CABG (the acronym has the same pronunciation as "cabbage"). CABG uses blood vessels in another part of the body (usually the chest, arms, and legs) to create a blood diversion. This diverts blood around one or more occluded segments of the artery and transports it to the myocardium [29] (**Figure 2(a)** & **Figure 2(b)**).

2.8. Effect of Nerve Function

Cholesterol is a structural component of cell membranes and is most abundant in the brain. Cholesterol is essential for normal nerve function. Elevated blood cholesterol levels are very common and associated with various neurological disorders. Neuronal cholesterol levels affect the function of G protein-gated inward potassium channels (GIRKs) [30]. Atorvastatin controls high cholesterol and normalizes the effects of neurotransmitters in the brain.

High cholesterol induces apoptosis and autophagy through the ROS-activated AKT/FOXO1 signaling pathway in tendon-derived stem cells. High cholesterol cause weakening of the tendons, it increases the risk of tendon pain and tendon rupture due to loosening of collagen fibrils [31] (**Figure 2(a)** & **Figure 2(b)**).

2.9. Cognitive Impairment

Hypercholesterolemic mice developed cognitive deficits as evidenced by object recognition memory tests. Cholesterol accumulation has been observed in four

different brain regions, including cortex, striatum, hippocampus, and substantia nigra, along with a significantly damaged blood-brain barrier due to hypercholesterolemia [16]. There is a complex relationship between hypercholesterolemia (elevated plasma cholesterol levels) and brain function. Since cognitive impairment, decreased brain acetylcholinesterase activity, mitochondrial dysfunction and inflammation are the main pathogenesis of neurodegenerative diseases, this result suggests that hypercholesterolemia is a potential risk factor for brain dysfunction [32] (**Table 5** & **Table 6**).

Cholesterol is one of the essential intrauterine factors required for fetal growth and development. High maternal cholesterol levels are known to affect the health of children. A high-cholesterol maternal diet adversely affects bone development in offspring and downregulates Hedgehog signaling in osteoblasts [33]. Cholesterol is an important component of eukaryotic membranes and helps regulate transmembrane signaling, cell-cell interactions and ion transport. Dysregulation of brain cholesterol levels can lead to neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease [34].

3. Myocardial Infarction

A heart attack, also colloquially called a heart attack, is a medical emergency. A heart attack occurs when blood flow to the heart is severely restricted or blocked. This happens very suddenly because the blood clot blocks blood flow to the heart and the lack of oxygen interrupts the activity of the heart muscle. Blockages are usually caused by the accumulation of fat, cholesterol, and other substances within the arteries of the heart (coronary arteries). Fatty deposits containing cholesterol are called plaques. The process of plaque formation is called atherosclerosis. In some cases, plaques can rupture and form clots, blocking blood flow. Poor blood flow can be caused by a variety of factors, but usually he is associated with blockage of one or more of the arteries of the heart. With no blood flow, the affected heart muscle begins to weaken. Time is of the essence in treating heart attacks, and even a few minutes of delay can lead to permanent heart damage or death. If blood flow is not restored quickly, a heart attack can cause permanent heart damage and death. Without blood, tissues lose oxygen and die (**Figure 3**).

Symptoms include difficulty breathing, pressure or pain in the chest (angina), neck, back, or arms, as well as fatigue, drowsiness, heart rhythm irregularities, and anxiety. The pain starts in the chest and spreads (or radiates) to other areas such as the left arm (or both arms), shoulder, neck, jaw, back, or down toward the waist. There are also secondary symptoms such as trouble sleeping (insomnia), nausea, and stomach problems. Heart attacks are often confused with indigestion, heartburn, palpitations, dizziness, and profuse sweating [35].

A heart attack can be diagnosed through a physical exam in which the pulse, blood oxygen level, and blood pressure are tested, and a competent cardiologist listens to the patient's heart and lung sounds. Diagnosis is also made by knowing the patient's medical history, where in the family the problem began, and the

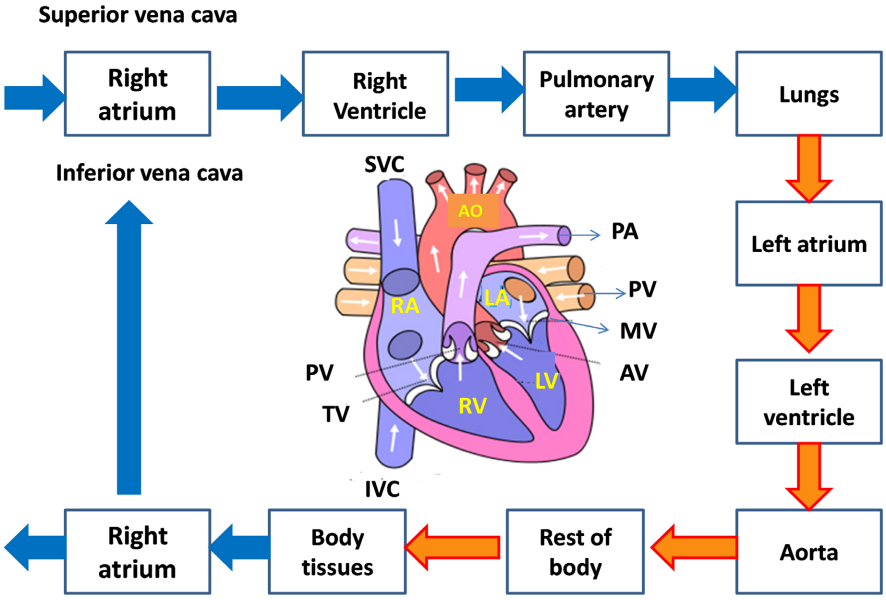

Figure 3. Circulation of blood through four chambered human heart.

patient's personal experiences. A blood test uses cardiac troponin to check for troponin in the bloodstream. A blood test that looks for this marker is one of the most reliable ways to diagnose a heart attack. The ECG also provides information about the accuracy and status of electrical events in the muscles, helping diagnose heart attack symptoms. An echocardiogram uses ultrasound (high-frequency sound waves) to make pictures of the inside and outside of the heart. Angiography shows areas with little or no blood flow. Computed tomography is performed to detect heart problems. An MRI uses a powerful magnetic field and computer processing to create images of the heart. Similar to angiography, these scans involve injection of radioactive dye into the blood [36]. The difference from angiography is the use of computer-assisted techniques such as computed tomography (CT) and positron emission tomography (PET) [37].

3.1. How to Reduce Risk of Cardiac Failure

There are many factors that increase the risk of heart failure. Few of these are detectable, but most are uncontrolled. However, there are ways to reduce the risk of heart attack. Important factors include diet, physical activity, age, structural deformation of blood vessels, myocardium, valve dysfunction, stress, obesity, hypertension, diabetes, medications, emotions, anxiety and noise pollution. To live a healthy life, we need to monitor calorie intake, expenditure, nutritional structure, sleep, natural cycles and circadian regularity. Regular monitoring of blood pressure, blood sugar, cholesterol, etc., should be followed by yoga and aerobics to improve fitness. It can test for problems related to blood circulation that can be detected by Airist. An annual test can detect many early warning signs of heart disease, including those you may not feel yourself. Hot drinks, red meat, tobacco and e-cigarettes are strictly prohibited. Exercise at least 45 mi-

nutes a day and eat healthy. Followed by yoga practice, deep breathing and meditation as I try to control my weight and reduce stress by living with nature. Stay calm, quiet, and live in a low-noise environment. Being vegetarian is a good option. Automatically start controlling high cholesterol, high blood pressure and diabetes. Reduce your intake of excess salt in your diet. There is a consistent and positive association between dietary sodium intake and induction of hypertension. This rate is significantly higher in Japan, where it exceeds 400 millimoles/day, whereas primitive societies consume less than 60 millimoles/day and do not have hypertension. High blood pressure can be controlled with a significantly reduced salt diet less than 10 millimoles/per day.

3.2. Diagnostics

Numerous biomarkers are available to predict cardiovascular risk in order to properly diagnose disease. They play an important role in predicting risk, its nature and morbidity individually or in combination [36]. There are both diagnostic and therapeutic markers. Diagnostic markers include lipid profile, glucose levels and hormone levels. In addition, these physiological biomarkers include serum ferritin, triglyceride to HDLp (high-density lipoprotein) ratio, lipopholin to cholesterol ratio, lipid to lipopholin ratio, LDL cholesterol levels, HDLp and apolipoprotein levels, lipopholin to LTP ratio, sphingolipids and omega-3 index and ST2 levels are also routinely used in the diagnosis of cardiovascular disease [38] [39]. It is true that there is a need for a faster and more authentic method for the rapid diagnosis of cardiovascular disease, heart failure (heart failure), and various lipid abnormalities and disorders in the [39] (**Table 5** & **Table 6**).

3.3. Lipid Profile

Lipid profile is highly important to know the presence normal and abnormal levels of cholesterol. Lipid profile tells about normal or falls into a borderline-, intermediate- or high-risk category cholesterol level. Lipid profile is carried out to assess the cardiovascular risk, its type and associating factors. If patient has attained the age of 45 years for males and 50 years for females, it is highly important to have lipid profile to know cholesterol levels and additional risk if the patients is smoker, obesity, high blood pressure (hypertension) diabetes and any heart related deformity. Children can also have high cholesterol, so your child may need a lipid panel blood test. Cholesterol levels in children are linked to three factors: heredity, diet and obesity. In most cases, kids with high cholesterol have a parent who also has elevated cholesterol.

Lipid profiles are very important for detecting the presence of normal and abnormal cholesterol levels. A lipid profile provides information about whether cholesterol levels are normal or fall into the borderline, intermediate, or high-risk categories. A lipid profile is performed to assess cardiovascular risk, its nature, and associated factors. When a patient reaches age 45 in men and 50 in women, a lipid profile can be obtained to know cholesterol levels and additional risks if

the patient is a smoker, obese, hypertensive (hypertensive) or diabetic. Very important and heart disease is associated with deformity. Children may also have high cholesterol levels, so blood tests for lipids may be needed. Children's cholesterol levels are determined by three factors: genetics, nutrition, obesity. In most cases, children with high cholesterol have parents who also have high cholesterol.

In most cases, the non-fasting lipid profile is more useful in predicting adverse cardiovascular outcomes. However, there is a correlation between fasting and non-fasting lipid profiles, especially cholesterol, triglycerides, HDL and LDL levels. Triglycerides varied the most in both men and women, with a mean difference of 8 mg/dL in men and 12 mg/dL in women, whereas mean differences in HDL were 1 mg/dL in women and 3 mg/dL in women. This is further classified as normal, diabetic, dyslipidemia, and hypertensive. More generally, non-fasting lipid profiles do not show significant differences from fasting lipid profiles containing triglycerides (**Table 3**).

Atherosclerosis is the underlying cause of heart attack and stroke. Early observations that cholesterol was a major component of arterial plaque gave rise to the cholesterol hypothesis for the pathogenesis of atherosclerosis. Population studies have shown that elevated levels of LDL cholesterol and the major structural protein of LDL, apolipoprotein B (apoB) 100, are directly associated with the risk of atherosclerotic cardiovascular events (ASCVE). I'm here. Indeed, the infiltration and retention of apoB-containing lipoproteins in the arterial wall is an important trigger that provokes an inflammatory response and promotes the development of atherosclerosis. Arterial injury causes endothelial dysfunction, promoting modification of apoB-containing lipoproteins and monocyte infiltration into the subendothelial space. Macrophage inflammation results in increased oxidative stress, increased cytokine/chemokine secretion, increased LDL/residual oxidation, endothelial cell activation, monocyte recruitment, and foam cell formation. Cholesterol efflux from macrophages to HDL plays an important role in preventing the development of atherosclerosis. HDL, apoA-I, and endogenous apoE prevent inflammation and oxidative stress and promote cholesterol efflux to reduce lesion formation. Lowering LDL-C with statins reduces the risk of cardiovascular events, providing ultimate evidence for the cholesterol hypothesis [38] (**Table 5** & **Table 6**) (**Figure 3**).

Cholesterol and triglycerides are insoluble in water, so these lipids must be transported with the protein. Lipoproteins are complex particles with a central core containing cholesterol esters and triglycerides surrounded by free cholesterol, phospholipids and apolipoproteins that facilitate lipoprotein formation and function. Immunohistochemistry, oxidative stress, inflammation, anatomic, imaging, genetic, and therapeutic biomarkers are also used for more comprehensive studies, depending on their specificity and scope. Emerging risks have been found to be associated with low-level and micro-level factors, and early diagnosis may reveal cardiovascular disease, thus requiring more serious interventions to confirm disease. There is an urgent need for new diagnostic and thera-

peutic markers that are adequate and reliable. It is time enough to start clinical support for patients [38] [40] (Table 5 & Table 6).

4. Therapeutics

4.1. Clinical Methods

The incidence of coronary heart disease is lowest in populations following a high-carbohydrate diet. These are complex carbohydrates, mainly polysaccharides of plant origin, that reduce the risk of CHD. Neither high-carbohydrate nor high-sucrose diets induced atherosclerosis in animals. An inverse relationship between fiber intake and CHD risk has also been observed. Treating a heart attack means restoring blood flow to the affected heart muscle as quickly as possible. This can be done in a variety of ways, from medications to surgery. Some of the methods below are very likely to be used for treatment. People who have difficulty breathing or have low blood oxygen levels are often given supplemental oxygen in addition to other heart attack treatments. Oxygen can be given through a tube just below the nose or through a mask that covers the nose and mouth. This increases the circulation of oxygen in the blood and eases the heart. Anticoagulants such as aspirin and other blood-thinning drugs are given to reduce the risk of heart attack and severe pain. Nitroglycerin is used to relieve chest pain. Blood vessels dilate or relax, allowing blood to flow more easily. Heart attacks can often cause disturbances in the normal heart rhythm, so-called arrhythmias, which can be life-threatening. Arrhythmia drugs can stop or prevent these disorders. Morphine is the most common pain reliever used to treat heart attacks. This will help relieve chest pain (Table 6).

Since lipids such as cholesterol and triglycerides are insoluble in water, these lipids must be transported in the circulation along with proteins (lipoproteins). Extra lipids obstruct blood flow, severely affect heartbeat rate mainly commencement of the next beat. A net difference in diastole, the systolic pressure cardiac cycle and muscle function (Figure 4). To avoid toxicity, large amounts of dietary fatty acids must be transported as triglycerides. These lipoproteins

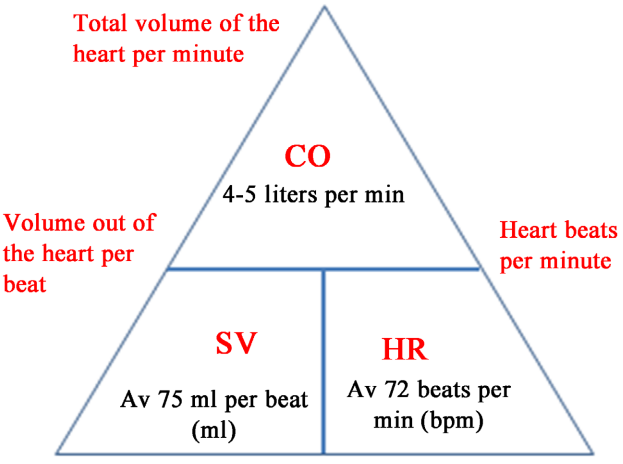

Figure 4. Normal cardiac cycle and heart beat rate.

play important roles in the absorption and transport of dietary fat through the small intestine, the transport of lipids from the liver to peripheral tissues, and the transport of lipids from peripheral tissues to the liver and intestine (reverse cholesterol transport). A secondary function is to absorb toxic foreign hydrophobic and amphiphilic compounds such as bacterial endotoxins from areas of invasion and infection [41]. However, to reduce high cholesterol, reduce your animal fat intake by 100%, use PUFAs in your diet, and use natural plant-based antioxidants. Although there are many ways to lower or balance cholesterol levels, proper diagnosis is very important [42] (**Table 6**).

4.2. Use of Lipid-Lowering Agents

Lipid-lowering drugs include 3-hydroxy-3-methylglutaryl-coenzyme-A (HMG-CoA) reductase inhibitors, bile acid sequestrants, cholesterol absorption inhibitors, fibrates, nicotinic acid derivatives, omega-3 fatty acid market [43]. U.S. Food and Drug Administration (FDA) guidelines have been established for dose ranges, indications, and evidence of clinical benefit (**Table 6**).

4.3. HMG-CoA Reductase Inhibitors (Statins)

Statins are utilised as first-line therapy because they effectively inhibit patient HMG-CoA reductase. Statins are often prescribed medications that efficiently demonstrate lipid-reducing capabilities, both in lowering LDL-C levels and in the prevention of CV events. Statins slow the rate at which cholesterol is synthesised. Statins function as competitive inhibitors of HMG-CoA reductase because of their structural resemblance to HMG-CoA, a precursor to cholesterol. Depending on the agent chosen and the baseline lipid profile, statins reduce LDL-C by 24% to 60% and triglycerides (TGs) by 5% to 50% (percentages are based on the various package inserts). Additionally, statins have a range of anti-inflammatory actions outside than reducing LDL-C, which may help with the clinical benefit in CVD, particularly in the early stages [44] (**Table 6**).

4.4. Bile Acid Sequestration

Bile acids are heterogeneous group of amphiphilic steroidal molecules. The steroidal core of bile acids is attached to cholesterol ring. If bile acids sequestrants are by using certain used to bind bile acids in the intestine, it can limit absorption of cholesterol and other lipids, and reduce the excess amount of cholesterol. The uptake of bile acids by intestinal epithelial cells modulates the activation of cytosolic and membrane receptors such as the farnesoid X receptor (FXR) and G protein-coupled bile acid receptor 1 (GPBAR1), which has a profound effect on hepatic synthesis of bile acids as well as glucose and lipid metabolism [45]. This increase in LDL receptors on hepatocytes and the elimination of LDL-C from the circulation are both brought on by the decrease in the amount of readily accessible cholesterol. The use of bile acid sequestrants is advised which reduce LDL-C level by 15% to 30% and raise HDL-C by 3% to 5% [45] (**Table 6**).

4.5. Nicotinic Acid Derivatives

Niacin lowers the synthesis of VLDL-C in the liver, which lowers the generation of LDL-C. Niacin at pharmacologic levels (1.5 - 2 g/day) reduces TGs and LDL-C by 15% - 20% and 30% - 40%, respectively, and raises HDL-C by 15% - 25%. Niacin is combined with other lipid-lowering medications as a second-line therapy. The most frequent adverse reactions are pruritis and vasodilation with flushing, both of which are typically dose-limiting. Other negative effects include dyspepsia, stomach ulcers, hyperuricemia, palpitations, and peripheral neuropathy, which occurs seldom. Patients with diabetes mellitus are treated using this [46]. Hepatotoxicity, a dangerous side effect that can occasionally lead to fulminant liver failure, has also been linked to the use of niacin, especially in older formulations [47] (**Table 6**).

4.6. Fibrates

The peroxisome-activated receptor is found in the muscle, liver, and other tissues. Fibric acid derivatives, or fibrates, such as gemfibrozil and fenofibrate, are agonists of this receptor. Fibrates can reduce TG levels by up to 50%. When treating patients with hypertriglyceridemia (TG > 400 mg/dL), they are regarded as the first-line medications. LDL-C reduction, however, varies amongst patients (10% - 15%; some had elevated levels). Patients with very high baseline TG levels may see an increase in HDL-C levels of up to 25% [48]. For fenofibrate and gemfibrozil, rash and dyspepsia are the most frequent side reactions, respectively. Gallstone risk may be raised by any fibrates. Additionally, it has been demonstrated that gemfibrozil raises the plasma concentration of statins, raising the danger of muscle damage [49] (**Table 6**).

4.7. Cholesterol Synthesis Inhibitors

Few of them are statins, fibrates, niacin, and ezetimibe that altogether decrease the hazard of atherosclerotic morbidities. These are built up home grown drugs utilized in CVD medications. There are vital approaches such as restraint of proprotein convertase, hindrance of the blend of apolipoprotein (apo) B and microsomal triglyceride exchange protein to piece the arrangement of atherogenic lipoproteins which happens is atherosclerosis. Other approaches are hindrance of adenosine triphosphate citrate lyase to restrain the blend of cholesterol, hindrance of the blend of lipoprotein, apoC-III to decrease triglyceride-rich lipoproteins, and cholesteryl ester exchange protein to upgrade high-density lipoprotein (HDL) usefulness [50]. Plant normal items repress cholesterol retention in mice and lower down plasma add up to cholesterol and triglyceride (TG) levels [51]. As with bile corrosive sequestrants, ezetimibe restrains the assimilation of cholesterol. It happens at the brush border of the little digestive system, and to arbiter of cholesterol assimilation. It makes bile corrosive sequestration, subsequently diminishing the accessibility of LDL-C, ezetimibe. It moreover actuates LDL receptor upregulation driving to expanded take-up of LDL-C into

cells, advance bringing down circulating LDL-C levels [52] (**Tables 6-8**).

5. Dietary Therapeutics

5.1. Daily Meals/Diets Rich in Omega-3 Fatty Acids

Daily meals/diets rich in omega-3 fatty acids significantly lower down the risk of CVDs risk. Use of omega-3 fatty acids causes reductions in TGs of up to 45% in

Table 7. Therapeutic methods used for treatment of high cholesterol disorders.

Name	Drug/chemical	Action mechanism	References
Lipid-lowering agents	Statins	Inhibits cholesterol synthesis hydroxy-3-methylglutaryl-coenzyme-A (HMG-CoA) reductase inhibitors lowering LDL-C levels and in the prevention of CV events	[44]
Bile acid sequestrants	Colesevelam, cholestyramine	Bind bile acids in the intestine, it can limit absorption of cholesterol and other lipids, and reduce the excess amount of cholesterol	[45]
Nicotinic acid derivatives	Niacin	Niacin lowers the synthesis of VLDL-C in the liver, which lowers the generation of LDL-C. It reduces TGs and LDL-C by 15% - 20% and 30% - 40%, respectively, and raises HDL-C by 15% - 25%.	
Fibrates	Gemfibrozil, fenofibrate	Agonists of peroxisome-activated receptor, TG levels by up to 50%, increase HDL-C level	[48]
Cholesterol absorption inhibitors	Statins, fibrates, niacin, and ezetimibe	Arbiter of cholesterol assimilation. bile corrosive sequestration, decrease triglyceride-rich lipoproteins	[50] [51] [52]
Omega-3 fatty acid (PUFAs	Eicosapentaenoic acid and docosahexaenoic acid	Cause reductions in TGs of up to 45% in patients	[53] [54] [55]
Natural anti-oxidants	Flavonoids, phenolic oligomeric proanthocyanidins (OPC) and pterostilbene	Lipid peroxidation, decrease cellular damage and contribute cardioprotective activity, of serum LDL-cholesterol (5.6%) and TG (12.5%)	[56]-[61]

Table 8. Showing drugs which are used to treat high cholesterol levels.

Drug class	Generic	Side effects
Statins work in the liver to prevent cholesterol from forming.	Lipitor (atorvastatin), Lescol (fluvastatin), Zocor (simvastatin), Crestor (rosuvastatin calcium)	Diarrhea, upset stomach, muscle and joint pain
PCSK9 inhibitors interact with a liver protein to lower LDL.	Repatha (evolucumab) and Praluent (alirocumab)	Back pain, symptoms of cold or flu
Selective cholesterol absorption inhibitors prevent cholesterol from being absorbed in the intestine.	Zetia (ezetimibe)	Diarrhea, tired feeling, headache, stomach pain, back pain
Bile acid sequestrants or bile acid-binding drugs work in the intestine to increase cholesterol disposal.	Questran (cholestyramine), Colestid (colestipol), WelChol (colesvelam)	Constipation, stomach pain, gas, indigestion, diarrhea

*Source: National Institutes of Health and National Health, Lung and Blood Institute.

patients [53]. Besides reduction in TGs, it increases the level of HDL-C by 10%. The addition of omega-3 fatty acids to statin therapy increased beta oxidation. Most vegetable oils are unstable during storage or cooking due to the oxidation of their polyunsaturated fatty acids. Therefore, partial hydrogenation is frequently applied to improve the flavor and oxidative stability of vegetable oils by reducing the content of the highly unsaturated linolenic and linoleic acids [54] [55]. Vegetable oils contain predominantly unsaturated (light, liquid) fatty acids of two kinds: monounsaturated (oleic acid—mainly in extra virgin olive oil) and polyunsaturated (linoleic acid and linolenic acid—in oils extracted from oil seeds). Plant origin short-chain omega-3 fatty acids are ALA (alpha-linolenic acid) mainly EPA eicosapentaenoic acid and DHA docosahexaenoic acid extend big health benefits. These are extracted from flaxseed [54] [55]. Besides plant oils "Fish oil" are also nutritionally and medically important as they contain long chain polyunsaturated fatty acids. Omega-3 fatty acids are found in fatty layers of cold-water fish and shellfish, plant and nut oils. Fish is low in saturated fat. These provide benefits to cardiovascular disease patients [54] [55] (**Table 9**).

5.2. Use of Natural Antioxidants

Plants contain natural antioxidants mainly flavonoidsm phenolic oligomeric proanthocyanidins (OPC) and pterostilbene (PT) with niacin (NA). These natural antioxidants blends show potential antihyperlipidemic effects and assist in reduction in lipid peroxidation, decrease cellular damage and contribute cardioprotective activity [56]. This is the main reason that medicinal plants constitute a principal health care resource. Due to their multitarget therapeutic action, there is a gradual increase in acceptance at the global level. Today there are number of herbal medicines are used for treatment of hyeprcholestmia and cardiovascular problems mainly CVDs. There are confirmed scientific reports on usage of herbal medicines which prove their therapeutic efficacy. These simple natural antioxidants blends present in drug formulations can help in mitigating chronic illnesses in general populations (**Table 9**).

Vegetables and fruits are rich in polyphenols, carbohydrates, vitamins, pigments and minerals. These act as natural antioxidants and assist in prevention of hyperhomocysteinemia. Fresh fruit, vegetable juice herbal tea improve cardiovascular health [57]. These are strong antihypercholestrolemic and antilipidemic perspectives in decrease of serum LDL-cholesterol (5.6%) and TG (12.5%) was also observed after consumption of T3 at day 60 [58] [59]. Blue-Green Alga (*Nostoc commune*) inhibits cholesterol absorption in mice and lowers down plasma total cholesterol and triglyceride (TG) levels compared with controls [60]. Interestingly, kombucha inhibit absorption of LDL-cholesterol and triglycerides and cause a significant increase in HDL-cholesterol life [61]. Both zedoary (*Curcuma zedoaria* Roscoe.) and *Xanthium strumarium* L. (Asteraceae) plant extracts showed antilipidemic effects [62] (**Table 9**).

Table 9. Showing anti-hyperlipidemic effects of plant natural products.

Plant Common name	Scientific name	Plant part extracts/compound	Biological activity
Anar	*Punica granatum* L.	Seeds	Antidiabetic and antilipidemic activities
Abu Jahl's melon	*Citrullus colocynthis* (L.) *Schrad*	Leaf extract	Antilipidemic activities
Araṇi or Agnimanthā	*Premna integrifolia* Linn.	Roots	Anti lipid peroxidation
Anjeer	*Ficus carica*	Leaves	Antilipidemic and antidiabetic effects of ficusin isolated from
Amur Rose	*Rosa davurica Pall.*	Fruit	Prevent the lipid peroxidation
Bayenge, Bisako, Elyi Ya Bakpala	*Gouania longipetala*	Methanol leaf extract	Antilipidemic activities
Common wireweed	*Sida acuta Burm. f.*	Leaves	Oxygen species/nitrogen species
Castor aralia	*Kalopanax pictus*	MeOH extract of stem barks,	Anti-lipid peroxidative effect
East Asian arrowroot	*Pueraria thunbergiana*	Leaves	Anti-lipid peroxidative effect
Fungi	*Bipolaris sp.and Phoma sp. sorokiniana*	Flavonoid and phenolic contents	Higher radical scavenging and anti-lipid peroxidation activity
Wild garlic	*Allium ursinum*	Allicin	Decrease hepatocyte cholesterol synthesis *in vitro*
Kali mirch, black piper	*Piper trioicum* Roxb.	Essential oil, seed	Anti lipid peroxidation activity of
Karela, bitter guard	*Momordica charantia*	Fruit extract Linn.	Significant lowering of cholesterol and triglyceride levels while elevating HDL-cholesterol levels
Tutsan or sweet-amber	*Hypericum androsaemum* L	Flower and leaf, phenolics and flavonoids	Antilipidemic activities
Rhubarb	*Rhizoma rhei, Rheum palmatum*	Leaves, anthraquinones	Reduce blood levels of total cholesterol, triglycerides, HDL and LDL
Indian gooseberry, emblic myrobalans, and Amla	*Phyllanthus emblica leaves*	Methanol extract, alkaloids, tannins, polyphenols, multi-vitamins and inorganic compounds	Antilipidemic activities
Oregon grape	*Mahonia aquifolium*	Berberine, beta-naphthoflavone a major isoquinoline alkaloid	Suppression of CYP1A expression and lipid-peroxidation
Arjun and lavang	*Terminalia arjuna (Roxb.)* Wight & Arn, and *Curcuma longa Linn extracts*	Bark	Anti-lipid peroxidative effects on serum and platelets *in vitro*
Harad, or Haritaki	*Terminalia chebula Retz.*	Fruit	Anti-lipid peroxidative,
Mandarin, cudrang, melon berry	*Cudrania tricuspidata*	Root bark flavonoids	Anti-lipid peroxidation efficacy on human low-density lipoprotein
Tomato	*Solanum lycopersicum*	Tomato paste, Lycopene	Anti-lipid peroxidative,

Continued

Indian atalantia	*Atalantia ceylanica*	Plant extract	Anti-lipid peroxidation
Dedaru Chisocheton	*Chisocheton ceramicus*	limonoids, erythrocarpines	Ceramicine B, a limonoid with anti-lipid droplets accumulation activity from
Dogbane or Indian hemp	*Apocynum venetum*	Leaves	Anti-oxidant and anti-lipid peroxidation effects
Italian buckthorn	*Rhamnus alaternus*	Leaves and flowers	Anti-lipid peroxidation
Hairy agrimony	*Agrimonia pilosa*	Leaves	Natural antioxidant sources, prevent oxidation-related diseases
Sweet basil	*O. basilicum*	Leaves	Anti lipid peroxidation effects, potent antioxidant effects
Sapphire-berry	*S. cochinchinensis* laurina (Retz.)	Bark methanolic extract	Antilipidemic activities
Spanish jasmine	*Jasminum grandiflorum* Linn.	Leaves and flowers, essential oil	Chemopreventive efficacy and anti-lipid peroxidative potential
Stonebreaker or Bhumiamla	*Phyllanthus urinaria*	Leaves and fruits	Anti-lipid peroxidation
Tulu	*Salacia oblonga* Wall.	Leaves	Hypoglycaemic and anti-oxidant activity
Zingiber officinale	Ginger	Underground stem, gingerols, shogaols, and paradols	Lipid peroxidation chemopreventive potential

5.3. Use of Herbal Drugs

The use of medicinal herbs is highly effective alternative treatment approach for several diseases including CVDs. In last two decades use of herbal preparations has been increased because of their therapeutic efficacy. Herbal preparations and drugs are cost-effective and show big therapeutic promise compared to standard modern therapies. Due to their easy usage and less toxic there is a general belief among people that they are safe. Polyherbal formulations prepared by using different proportions of *Commiphora mukul* (Hook ex Stocks) Eng., *Salacia reticulata* Wight, *Terminalia arjuna* (Roxb.) Wight & Arn, and *Curcuma longa* Linn showed anti-lipid peroxidative effects [63]. Today statins and biguanides are two prominent representatives of natural products which are mostly used against metabolic disease (**Table 8**). There is going on a large search for lipid-modifying agents. Various types of herbs can potentially reduce serum lipid levels through different metabolic pathways. Morespecially, the herb-drug interactions decrease the level of morbidity and show very significant anti-hyperlipidemic effects [64] (**Table 8**).

5.4. Antihyperlipidemic and Anti-Lipid Peroxidation Agents

Several species of terrestrial plants synthesize and possesses anti-lipid agents. Dietary use of *Aloe vera* juice lower down LDL cholesterol levels by 45%, 3% and

69% [65]. Similarly, raw onion *(Allium cepa* L.) significantly cut down the cholesterol level, hypertension and diabetes [66]. Anti-lipid peroxidation has been also identified *Phyllanthus emblica* leaves [67], Tunisian *Zizyphus lotus* Mkadmini [68], *Terminalia chebula* Retz. fruits [69], *Hypericum x moserianum* and *Hypericum ericoides* [70]. Use of *Aegle marmelos* (AMFEt), and *Momordica charantia* (Linn.) and tomatoes significantly cut down 3% or 9% serum TC and LDL levels [71] [72] (**Table 9**).

Garlic shows multiple protective effects and improves functioning of cardiovascular system [73] [74] [75]. It removes off atherosclerosis and does reduction of serum lipids [75]. It shows inhibition of platelet aggregation and enhancement of fibrinolysis. Wild garlic (*Allium ursinum*) has been reported to contain similar amounts of sulfur-containing compounds [76], thiosulfinates and ajoenes from garlic, exert similar effects on cyclooxygenase, 5-lipoxygenase, angiotensin converting enzyme, and platelet aggregation [77], DADS shows strong antilipidemic effects [78] (**Table 7**).

Onion derived sulfur-compounds, including S-methyl cysteine sulfoxide and allylpropyl disulfide [79], showed hypolipidemic effects. These are established in rats and rabbits, and lower down effects of diet-induced atherosclerosis, maintain hypolipidemic action, and inhibitory effects on platelet formation [80]. Raw onion contains these compounds in ample amount and antithrombotic effects [80] (**Table 9**).

***Bel* (*Aegle marmelos*)**

A. marmelos leaf extract shows anti-hyperlipidemic activity in rats in a dose-dependent manner. It causes a significant reduction in total cholesterol, triglycerides, low-density lipoprotein, very-low-density lipoprotein, and significantly increased high-density lipoprotein life [81]. Its unripe fruits also show antidyslipidemic effect against ISO-induced cardiac stressed rats and restore ISO-induced myocardial infarction life [82] (**Table 9**).

Kareel (*C. decidua*)

Capparis decidua (CD) is a xerophytic or desert dominating shrub found in desert region of Rajasthan showing strong climatic adaptations. It is a densely branched, thorny plant with smaller scanty and caduceus leaves having pink to red flowers and green berry fruits. Its fruit and shoot extract possesses very strong hypolipidaemic efficacy and significantly cut down human plasma triglycerides, total lipids and phospholipids [83] [84] [85] (**Table 1**). Plant fruit shows antiatherosclerotic effect [86] (and its regular use can restore cardiovascular activity [87] (**Table 9**).

Toddalia aculeata

Toddalia aculeata is an important medicinal plant widely used for treatment of several diseases and disorders. Plant shows antihyperlipidemic activities in high fat diet fed hyperlipidemic rats [88]. Plant contains aculeatin that causes lipolysis of 3T3-L1 adipocytes [89] and assists in restoration of cardiovascular system [90]. Plant also acts as smooth muscle relaxant [91] (**Table 9**).

Ocimum sanctum

Tulsi (*Ocimum sanctum* Linn.) leaves show lipid-lowering and anti-oxidative activities [92]. It has also been shown to counter metabolic stress does normalization of blood glucose, blood pressure and lipid levels. Holybasil (tulsi) lowers fasting glucose and improves lipid profile [93]. It assists in relieving from psychological stress and exerts positive effects on memory and cognitive function through its anxiolytic and anti-depressant properties [94] (**Table 9**).

5.5. Cardioprotective Agents

Onions contain flavonoids which are used for prevention and treatment of cardiovascular diseases and stop heartburn [95]. Onion bulbs contain sulfur containing compounds thiosulfinates dimethyl- and diphenyl-thiosulfinate and its soup showed inhibitory activity against platelet aggregation [96] [97] [98]. Quercetin effects on platelet aggregation [99] [100] and decreases blood pressure in hypertensive subjects and show cardiovascular benefits [101]. Onion (*A. cepa*) leaves showed cardioprotective and antioxidant activity in doxorubicin-induced cardiotoxicity in rats [102] [103]. It restores and control ambulatory blood pressure and endothelial function in overweight-to-obese patients affected with (pre-)hypertension [104] [105] (**Table 3** and **Table 9**).

Almonds may increase circulating HDL cholesterol when substituted for a high-carbohydrate snack in an isocaloric diet, yet little is known about the effects on HDL biology and function. Substituting almonds for a carbohydrate-rich snack within a lower-saturated-fat diet may be a simple strategy to maintain a favorable circulating HDL subpopulation distribution and improve cholesterol efflux in normal-weight individuals with elevated LDL cholesterol [105] Antihyperlipidemic and cardioprotective effects of plant natural products [106] (**Table 9**).

The polyunsaturated fatty acids (e.g. linoleic and arachidonic acids) have an additional role that is to inhibit platelet aggregation and prevent thrombus formation. More often, arachidonic acid metabolises in the vascular endothelium to form to important metabolites, *i.e.*, prostacylin, and thromboxane. These two compounds have opposing effects on the cardiovascular system. Whereas, thromboxane induces platelet aggregation, prostacylin inhibit and prevent intravascular thrombus formation. Prostacylin was found also to relax coronary blood vessels, thus opposing the action of thromboxane. Generation of prostacylin is the biochemical mechanism underlying the well known ability of blood vessels to resist platelet aggregation. Linoleic acid from diet becomes the precursor of arachidonic acid that effectively works against CHD. Thus cholesterol level can be regulated by controlling the amount and type of fat in the diet, drugs and proper exercise (**Table 8** and **Table 9**).

6. Plant Pigments

6.1. Anthraquinones and Sulfur-Compounds

Anthraquinones isolated in ethanolic fractions of total *Radix rhizoma* rhei signifi-

cantly reduce blood levels of total cholesterol, triglycerides, HDL and LDL [106]. Gallic acid, a trihydroxybenzoic acid also demonstrates robust anti-obesity capabilities [107]. Utilization of niacin and ergosterol may prevent the hypercholesterolemia and incidence of coronary heart diseases [108] (**Table 1**). Similar anti-hyeprcholestemic effect is also reported in N-acetylcysteine (NAC) and sesame oil administration in diet-induced hypercholesterolemic mice [109]. Guar gum shows anti-hypercholesterolemia, anti-hyperglycemia and anti-obesity activity [110] (**Table 8**).

6.2. Flavonoid and Phenolic Compounds

Flavonoid and phenolic compounds found in *Hypericum androsaemum* L. (Hypericaceae) and *Bipolaris sp*. show significantly higher radical scavenging and anti-lipid peroxidation activity [111] [112]. Naringenin (NRG) the aglycone flavonoid found in grapefruits shows anti-lipid peroxidation activity [113]. Antioxidant and anti-lipid peroxidation activities are also reported in (+)-catechin, (−)-epicatechin, and procyanidin B2 [114], Berberine [115] (**Table 8**).

6.3. Lycopene

Lycopene is known to decrease cardiovascular risks. Madecassoside also show protective effect against myocardial ischemia reperfusion injury, and effects of anti-lipid peroxidation, [116]. Ginsenoside Rb1 and Rg1 isolated from *Cudrania cochinchinensis* var. gerontogea [117], naphthalenic compounds 6-methoxysorigenin and its glycosides [*i.e.*, 6-methoxysorigenin-8-O-glucoside, alpha-sorinin, and 6-methoxysorigenin-8-rutinoside] two acylates (peracetate and perpropionate) from *Rhamnus nakaharai* showed anti-lipid peroxidation activity [118]. *Capparis sicula* subsp. sicula and *Capparis orientalis* aerial parts showed antilipidemic activity due to presence of quercetin rutinoside (rutin) [119]. *C. cassia* contains coumarin, trans-cinnamic acid, cinnamaldehyde, 2-hydroxycinnamaldehyde, 2-methoxycinnamaldehyde (6), 2-hydroxy-cinnamyl alcohol, benzoic acid, (+)-syringaresinol and phenethyl (E)-3-[4-methoxyphenyl]-2-propenoate bio-organic compounds with antihyperlipidemic activity [120]. Quercetin (QUE) shows cardioprotective effects of against the damage induced by a high-cholesterol (HC) diet in hyperglycemic rats [7]. QUE attenuated cardiac diastolic dysfunction (increased E: A ratio), prevented cardiac cholesterol accumulation, and reduced the increase in HC-induced myocyte density [7] (**Table 8**).

Edible mushrooms *Ganoderma lucidum* contain bioactive compounds which showed promising effects on several cardiovascular risk biomarkers. *Ganoderma lucidum* constituents showed hypocholesterolemic, antidiabetic and prebiotic effects [121]. *Ganoderma lucidum* (GI) modulated genes correlated with Lactobacillus enrichment and the reduction of circulating cholesterol-derived fats. Use of GI extract effectively prevents metabolic disorders associated with hypercholesterolemia [122]. *Bifidobacterium longum* strains showed cholesterol-lowering effects in hypercholesterolemic rats [123]. It shows cholesterol assi-

milation ability, and expressions of key genes involved in cholesterol metabolism and alterations of gut microbiota. Blocking FSH inhibits hepatic cholesterol biosynthesis and reduces serum cholesterol and reduces the chances of hypercholesterolemia [124]. This new strategy is successful in menopause, particularly for women in peri-menopause characterized by FSH elevation only (**Table 8**).

7. Conclusion

This is well known fact that elevation in serum and plasma cholesterol is highly harmful for human health. Elevated cholesterol level is a major risk factor for CVD, the leading cause of death worldwide. It is very clear that extra cholesterol develops fatty deposits in your blood vessels which obstruct blood flow and create extra pressure inside heart and massively effect pumping of blood. High cholesterol is sneaky and silent. It suddenly evokes heart attack or stroke and gives rise series of cardio vascular problems. Obese, diabetic, and hypertension increase the risks of CHD manifold and give rise cardiacmyopathies. For significantly cut down the hyperlipidaemia, hypertension and diabetes eat fresh fruits, vegetables, wet seeds and fibrous diet. Use PUFAs, *i.e.*, polyunsaturated fatty acids (e.g. linoleic and arachidonic acids) in replacement of animal fats. PUFAs inhibit platelet aggregation and prevent thrombus formation. Make diet structure for daily consumption having onions, garlic, wet seeds, *Aloe vera*, citrus fruits, juice, vegetables, low salt and low sugar an isocaloric diet. Almonds help to cut down LDL cholesterol and increase circulating HDL cholesterol. Hypertension can be successfully treated with a drastically low sodium diet, *i.e.*, less than 10 mmol/day. Cholesterol sequestration and synthesis inhibitors have been proved high effective in hyper-cholestemic patients. Eating fresh fruits and vegetables, which are natural antioxidants, following a low-saturated-fat diet, and engaging in daily exercise is a simple strategy to maintain a favorable circulating cholesterol level. To reduce the risk of cardiovascular disease (CVD) events, it is advisable to completely avoid consuming hot drinks, red meat, tobacco, and vaping products. Additionally, practicing yoga, deep breathing exercises, and meditation can be highly beneficial in managing stress and maintaining weight control.

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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