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Hypercholesterolemia and its Management Using Various Bioactive Compounds: A Literature Review

(KAJIANPUSTAKA: HIPERKOLESTEROLEMIA DAN PENANGGULANGANNYA DENGAN MENGGUNAKAN BERBAGAI SENYAWA BIOAKTIF)

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ABSTRACT

Hypercholesterolemia is characterized by levels of total cholesterol and low-density lipoprotein (LDL) above normal. Hypercholesterolemia is a major risk factor for cardiovascular disease. This study was aimed to explore and analyze various bioactive compounds to manage hypercholesterolemia. Efforts to overcome the condition of hypercholesterolemia are to reduce the consumption of a diet rich in cholesterol and calories, and consuming contemporary hypercholesterolemic drugs such as statins, as well as by regulating the body's cholesterol metabolism with various antihypercholesterolemic bioactive compounds. Various findings of antihypercholesterolemic bioactive compounds have various sources and effects on cholesterol profiles. Bioactive compounds can be classified according to their mechanism of hypocholesterolemic action, which are inhibition of cholesterol absorption, inhibition of cholesterol biosynthesis, increased cholesterol excretion, increased cholesterol reverse transport, and increased cholesterol catabolism. Several bioactive compounds are involved in a dual mechanism. The development of these various bioactive compounds can be used as an alternative treatment for hypercholesterolemia since contemporary medicines have proven to have many side effects.

Keywords: Bioactive compounds; cholesterol; hypercholesterolemia

ABSTRAK

Hiperkolesterolemia ditandai dengan kadar kolesterol total dan *low-density lipoprotein* (LDL) di atas normal. Hiperkolesterolemia merupakan faktor risiko utama penyakit kardiovaskuler. Kajian ini bertujuan untuk mengeksplorasi dan menganalisis berbagai senyawa bioaktif untuk mengelola hiperkolesterolemia. Upaya mengatasi kondisi hiperkolesterolemia adalah dengan mengurangi konsumsi makanan yang kaya kolesterol dan kalori, dan mengkonsumsi obat hiperkolesterolemia terkini seperti statin, serta dengan mengatur metabolisme kolesterol tubuh dengan berbagai senyawa bioaktif antihiperkolesterolemia. Berbagai temuan senyawa bioaktif antihiperkolesterolemia memiliki berbagai sumber dan efek terhadap profil kolesterol. Senyawa bioaktif dapat diklasifikasikan menurut mekanisme aksi hipokolesterolemianya, yaitu penghambatan penyerapan kolesterol, penghambatan biosintesis kolesterol, peningkatan ekskresi kolesterol, peningkatan transpor balik kolesterol, dan peningkatan katabolisme kolesterol. Beberapa senyawa bioaktif terlibat dalam mekanisme ganda. Pengembangan berbagai senyawa bioaktif tersebut dapat digunakan sebagai alternatif pengobatan hiperkolesterolemia karena obat-obatan kontemporer terbukti memiliki banyak efek samping.

Kata-kata kunci: senyawa bioaktif; kolesterol; hiperkolesterolemia

INTRODUCTION

Cardiovascular disease is the number one cause of death in the world (Roth *et al.,* 2017). This disease was reported to have caused 17.9 million deaths in the world in 2016. These deaths were mostly caused by heart attacks and strokes. Based on the World Health Organization (WHO) report, cardiovascular disease causes an average of 12 million deaths annually worldwide (WHO 2021). One of the main risk factors for cardiovascular disease is hypercholesterolemia, which is characterized by cholesterol levels in the bloodstream exceed normal limits (Lee *et al.,* 2019).

Hypercholesterolemia is influenced by genetic factors and lifestyle aspects from an unbalanced diet and lack of physical activity (Febriani and Besral 2018). Dietary risk factors include excessive consumption of foods with high cholesterol and calories. Increased cholesterol levels in the body can also be caused by increased de novo cholesterol synthesis and high absorption of dietary cholesterol (Baila-Rueda *et al.,* 2016). Efforts in reducing the cholesterol levels can be done by lowering high cholesterol and calories consumption and modifying the body's cholesterol metabolism using dyslipidemia bioactive compounds (Ji *et al.,* 2019).

Efforts to overcome hypercholesterolemia are carried out by targeting a reduction in cholesterol levels, especially in the cholesterol fraction in the form of low-density lipoprotein (LDL) (Rosei and Salvetti, 2016). Synthetic drugs are contemporary therapeutic agents given in an effort to overcome hypercholesterolemia. The use of synthetic drugs, especially statins, is the first and most widely prescribed in dealing with hypercholesterolemia today (Suprapti 2018). Although the use of synthetic materials shows a fairly effective therapeutic effect, the emergence of side effects and the risk of resistance cannot be avoided. Many patients who use statins show the side effects of the treatment (Zodda *et al.,* 2018). The common side effects of statin are myalgia and rhabdomyolysis (Ramkumar *et al*., 2016).

The development of science and technology in the medical world has led to more and more research related to the discovery of various bioactive compounds with antihypercholesterolemic activities. Natural bioactive compounds include organic chemical compounds that can interact with one or more body components. These various bioactive compounds come from various types of living things, especially plants, fungi, animals, microorganisms and their metabolites that can be presented through food (Shrinet *et al.,* 2021). Some of these bioactive compounds offer antihypercholesterolemic effects with lower side effects and are proven to be well tolerated by the body (Ji *et al.,* 2019). These various bioactive compounds show variations in effectiveness and target mechanisms, for example, allicin (*Allium sativum*) (Frankel *et al.*, 2016), curcumin (*Curcuma longa*) (Panahi *et al.*, 2018), ginsenoside group (*Panax spp*.) (Liu *et al.*, 2018), salvianolic acid B (*Salvia miltiorrhiza*) (Qin *et al.*, 2019) and leoligin (*Leontopodium alpinum*) (Tauchen and Kokoska, 2016).

This review study was aimed to explore and analyze various bioactive compounds that showed effectiveness to overcome hypercholesterolemia. This study is also encouraged because of the increasing public preferences for natural medicines (Bahmani *et al.,* 2015). This study highlights cholesterol, cholesterol biosynthesis, hypercholesterolemia, contemporary anti-hypercholesterolemia drug, and various antihypercholesterolemic bioactive compounds: therapy, effects, and mechanism of activities. This study may be used as a reference for the development of alternative drugs and treatment strategies for hypercholesterolemia conditions.

Cholesterol

Cholesterol (3-hydroxy-5,6-cholestene) belongs to steroids. Steroids are lipophilic complex molecules with a four-ring structure joined together. These four rings are composed of three six-group rings and a five-group ring that forms a carbon skeleton called cyclopentanoperhydro-phenanthrene(Albuquerque *et al.,* 2019). Lipoproteins consisting of cholesterol and lipoproteins in the blood circulation are divided into several classes based on these physical and chemical parameters and are also related to their function (Ivanova *et al.,* 2017). Lipoproteins are generally divided into chylomicrons, high-density lipoprotein (HDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL). Chylomicrons are lipoproteins derived from the absorption of fat and cholesterol in the intestines for further transport to the liver and fat and muscle tissue. Molecules of HDL are

non-atherogenic, and have a function to take excess cholesterol in the blood circulation to be returned to the liver and excreted (Huff *et al.,* 2021). The VLDL is formed in the liver and functions to excrete triglycerides. The IDL is a lipoprotein in which some of the triglycerides have been removed. The LDL is the main particle that plays a role in the transport and storage of cholesterol and atherogenic lipids. About two-thirds of circulating cholesterol is carried by LDL molecules to peripheral tissues. The LDL is the final stage of VLDL catabolism in which most of the triglycerides have been removed (Jim 2014).

Cholesterol is an essential component of membranes that carries out various vital functions for cells. One of them is to form the fluidity of the membrane. The fluidity property allows cells to regulate their permeability to certain molecules to penetrate through the membranes. The importance of this function makes every cell accompanied by the ability to synthesize cholesterol. Cholesterol functions as a precursor molecule for the formation of steroid hormones in the form of cortisol, aldosterone, and adrenal androgens; sex hormones in the form of pregnenolone, estrogen, progesterone, and testosterone; formation of vitamin D; myelin sheath, dendrites, and neuron synapses; and bile (Huff *et al.,* 2021). Bile plays a role in the digestion, absorption, and excretion of lipids. In addition, cholesterol also plays an important role in signalling pathways of every eukaryotic cell. Through this signalling pathway, each cell can regulate the uptake and synthesis of cholesterol according to intracellular needs. If the conditions of intracellular cholesterol homeostasis are met and maintained, excess cholesterol will accumulate in the blood which results in a hypercholesterolemic condition (Yu *et al.,* 2019).

Cholesterol Biosynthesis

Cholesterol supply in the body can be sourced exogenously from absorption and/or endogenously from biosynthesis (Zhang *et al.,* 2019). Cholesterol is synthesized from a two-carbon intermediate molecule, namely acetyl-CoA which is linked to each other through a series of enzymatic reactions that ultimately form cholesterol which is a 27-carbon molecule. All lipid, carbohydrate, and protein catabolism can be directed towards cholesterol biosynthesis reactions.

Cholesterol biosynthesis consists of five main steps that occurs in the cytoplasm and the endoplasmic reticulum, namely: (1) Conversion of acetyl-CoA to 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA); (2) Conversion of HMG-CoA to mevalonate; (3) Conversion of mevalonate into isoprene molecules, namely isopentenyl pyrophosphate (IPP); (4) Conversion of IPP into squalene; and (5) conversion of squalene to cholesterol. The first step occurs in the cytoplasm while the remaining reactions occur in the endoplasmic reticulum (Shi *et al.,* 2022). Normally a healthy adult human body synthesizes cholesterol as much as 1 g/day and consumes approximately 0.3 g/day. Cholesterol levels that are maintained in the body are 150-200 mg/dL which are partially controlled through biosynthesis and partly through the absorption of cholesterol from the food consumed. The largest proportion of cholesterol used in the body is for the synthesis of bile acids (Sitaula and Burris, 2016).

Hypercholesterolemia and Its Risk

Hypercholesterolemia is a condition when the total cholesterol in the blood circulation exceeds normal levels. Total cholesterol is defined as the total amount of cholesterol in all lipoproteins circulating in the body (Glueck and Kereiakes, 2019). Normal total cholesterol values in humans is <200 mg/dL. In diagnosis, hypercholesterolemia is also defined when the level of the low-density lipoprotein (LDL) fraction increases beyond normal limits and the level of high-density lipoprotein (HDL) decreases. LDL and HDL are the main transporters of cholesterol in the body that have contrasting functions (Toori *et al.,* 2018).
Chronic high total cholesterol pathologically causes an imbalance condition. Imbalances in cholesterol homeostasis are triggered by increased food consumption or genetic factors. Cholesterol imbalance triggered by hypercholesterolemia begins to affect homeostasis from the cellular level. Normally, cells can detect conditions when intracellular cholesterol levels exceed normal limits mediated by receptors on the endoplasmic reticulum. The non-degradable nature of cholesterol causes cells to respond to high cholesterol levels by decreasing the rate of cellular synthesis, reducing influx, and increasing efflux (Röhrl and Stangl 2018).

When an individual increases the consumption of foods that are rich in cholesterol, there will be an increase in LDL levels in the

blood to be supplied to various tissues. If intracellular cholesterol requirements are met and shift the balance of cholesterol homeostasis, cells will limit further LDL influx to excrete excess cholesterol in the form of LDL into the blood circulation (Röhrl and Stangl 2018). Excess LDL in the blood circulation will be overcome by the presence of HDL which serves to return excess LDL to the liver to be excreted in the form of bile through a reverse cholesterol transport mechanism (Ouimet *et al.,* 2019). High levels of LDL in the blood circulation also have been shown to be a risk factor for atherosclerosis (Jiang *et al.,* 2022). Hypercholesterolemic conditions can also cause pathological conditions at the cellular level which are characterized by the emergence of membrane stiffness and results in a decrease in cell permeability (Glueck and Kereiakes, 2019).

Various Antihypercholesterolemic Bioactive Compounds: Therapy, Effects, and Mechanism of Activity

Various natural antihypercholesterolemic bioactive compounds and their effects on cholesterol profile have been discovered and studies (Table 1). The large variety of bioactive compounds shows their potential alternative treatments for hypercholesterolemia. Although the physiological effects provided by natural bioactive compounds are sometimes lower than synthetic drugs, these ingredients can be easily introduced into the diet with no or cause only a few minimum side effects (Scolaro *et al.,* 2018).

Most of the information sources regarding the antihypercholesterolemic effect of various bioactive compounds are obtained from experiments on small laboratory animals such as hypercholesterolemic rats and mice. Based on the sources, the bioactive compounds of anti-hypercholesterolemia that have been identified are mainly obtained from plants in the form of trees, shrubs, shrubs, lianas and herbs (Wresdiyati *et al.,* 2023). The parts of the plants that became the sources of extraction were mainly isolated from the fruits and leaves. In addition, some bioactive compounds were extracted from the tubers such as *Allium sativum* source of allicin (Frankel *et al.,* 2016), rhizome parts such as *Curcuma longa* source of curcumin (Panahi *et al.,* 2018) and *Panax spp*., source of ginsenoside group compounds (Liu *et al.,* 2018) roots such as *Salvia miltiorrhiza*, source of salvianolic acid B (Qin *et al.,* 2019) and plant roots of *Leontopodium alpinum* as a source of leoligin (Tauchen and Kokoska, 2016), parts from seeds such as in various types of oats as a source of β–glucan (Sima *et al.,* 2018), to parts from oils such as olive oil as a source of oleanolic acid and luteolin (Manzoor *et al.,* 2017). Several bioactive components are generally found in plants such as β-sitosterol which is a phytosterol constituent of plant cell membranes (Babu and Jayaraman, 2020).

Several antihypercholesterolemic bioactive compounds have been identified from animal sources such as chrysin which can mainly be isolated from propolis and honey (Olas 2020). In addition, there is a sterol type stigmasterol which is also found in unpasteurized milk. Sources of other antihypercholesterolemic bioactive compounds can be isolated from the fungal group. Ergosterol, a sterol that makes up cell walls in fungi can be obtained from various edible mushrooms and has been shown to have antihypercholesterolemic activity (He *et al.,* 2019). In addition, 26-oxygenosterol was isolated from the fungus *Ganoderma lucidum* (Hajjaj *et al.,* 2015), monaskin and ankaflavin isolated from the fungus *Monascus purpureus* (Lee *et al.,* 2018), and lovastatin which is a natural statin and can be isolated from *Cantharellus cibarius, Agaricus bisporus, Imleria badia, Lentinula edodes* (Kała *et al.,* 2020).

Various bioactive compounds with antihypercholesterolemic activity showed efficacy against cholesterol changes through certain mechanisms. Some components represent a single mechanism whereas others may exhibit more than one mechanism. Various antihypercholesterolemic mechanisms shown by these various bioactive compounds can be grouped into inhibition of cholesterol absorption (a) and cholesterol biosynthesis (b); and increased cholesterol excretion (c), cholesterol reverse transport (d), and cholesterol catabolism (e) (Ji *et al*., 2019).

Inhibition of Cholesterol Absorption.

The fat constituents of the diet are initially emulsified by bile acids to form water-insoluble fat globules called micelles. The emulsification process is important in increasing the surface exposure to lipase. Lipase plays a role in the hydrolysis of these fat globules into simpler fat constituents for absorption. Cholesterol absorption is transferred from the small intestine through the enterocytes to the lacteals. The absorption process mainly takes

place in the duodenum in the proximal part of the jejunum (Javaid *et al.,* 2018). Cholesterol absorption from dietary components and as a fraction of bile acids is mediated by the Niemann-Pick C1 Like1 membrane transporter protein (NPC1L1) located at the brush border. The NPC1L1 protein expression is regulated by transcriptor proteins such as sterol regulatory element-binding protein 2 (SREBP2) and hepatocyte nuclear factor 4α (HNF4α) (Kobayashi 2019).

Free cholesterol will be esterified into cholesterol esters by Acyl-CoA; cholesterol acyltransferase (ACAT) in the endoplasmic reticulum. Furthermore, cholesterol ester molecules together with triglycerides will be formed into chylomicrons, water-soluble fat globules which will be secreted into lymph vessels (Xiao *et al.,* 2019). The formation of chylomicrons is mediated by microsomal triglyceride transfer protein (MTTP). The MTTP is a protein that is also a secretory factor for ApoB100, the lipoprotein that composes VLDL, IDL, and LDL (Vallianou and Hadzopoulou-Cladaras, 2016).

Research on several bioactive components showed inhibitory activity on cholesterol absorption (Table 2). The mechanism shown varies with the stages of absorption from hydrolysis and transformation of molecules in the intestinal lumen to enterocytes. Variations in the mechanism are shown by stigmasterol and β-sitosterol, a sterol compound found in plants. Both of these bioactive components work as cholesterol competitors in micellar formation because their structure is similar to cholesterol molecules (Feng *et al.,* 2018). The β-glucan, a type of dietary fiber found abundantly in grains and fungi, has been shown to contribute to the inhibition of bile acid reabsorption by binding and inhibiting the formation of micelles with their thick, gel-like structure (Korolenko *et al.,* 2020).

Another inhibitory pathway involves the bile acid transporter in the ileum, the apical sodium bile-acid transporter (ASBT). The ASBT plays a role in reabsorbing most bile acids which then enter the enterohepatic pathway. The function of this reabsorption is to maintain the availability of bile acids in the intestinal lumen, which play a role in fat digestion and absorption (Dawson 2017). The inhibitory activity of this transporter has been shown to reduce the absorption of bile acids and fats in the intestine (Rao *et al.,* 2020). This activity has also been shown to reduce the cholesterol profile as found in the bioactive component of palmatin (Ning *et al.,* 2015).

Inhibition of Cholesterol Biosynthesis.

Various bioactive components showed variations in targeting inhibition cholesterol biosynthesis (Table 3). These variations include various catalyzing enzymes as well as genes encoding transcription factors involved in cholesterol biosynthesis. Inhibition of HMG-CoA reductase, a catalyzing enzyme that is a limiting factor in cholesterol biosynthesis, is the most common target among bioactive components. The HMG-CoA reductase is an effective target in lowering the cholesterol profile. The effectiveness of this target makes statins the leading line for the treatment of hypercholesterolemia (Gunasekaran and Shukor, 2020). Each bioactive component has variations in inhibiting HMG-CoA reductase. Some of the bioactive components work by inhibiting the expression of mRNA and protein from HMG-CoA reductase. Several other bioactive components inhibit the expression of HMG-CoA reductase by activating the AMP-activated protein kinase (AMPK) signalling pathway (Liu *et al.,* 2015). This mechanism was found in the bioactive compounds anthocyanin, berberine, ginsenoside-Rg1, ginsenoside-Rg3, and IH-901. Inhibition of HMG-CoA reductase can also occur directly by blocking its active site as found in leoligin compounds (Scharinger *et al.,* 2016).

Inhibition of enzymes directly involved in cholesterol biosynthesis was found in the bioactive components monaskin and ankaflavin, 26-oxygenosterol, and stigmasterol. Monaskin and ankaflavin inhibit the activity of acetyl-coenzyme A acetyltransferase (ACAT) in the liver. The ACAT or thiolase is an enzyme that plays a role in converting two units of acetyl-CoA into acetoacetyl-CoA in the early stages of cholesterol biosynthesis (Brown *et al.,* 2021). The 26-oxygenosterol exhibits inhibition of lanosterol 14α-demethylase, the enzyme that catalyzes the biotransformation of 24,25-dihydro-lanosterol to cholesterol (Hajjaj *et al.,* 2015). Stigmasterol inhibits sterol 24-reductase, an enzyme that catalyzes the transformation of desmosterol to cholesterol in the final stages of cholesterol biosynthesis (Körner *et al.,* 2019).

Inhibition of the fatty acid biosynthetic pathway was found in naringenin and jatrorrizin.

Table 1. Various antihypercholesterolemic bioactive compounds

Bioactive compounds	Main Isolation Source	Effects on Lipid Profile	Research Subject	References
26-oxygenosterol	*Ganoderma lucidum*	↓TC, ↓TG, ↓LDL	Rats	(Hajjaj *et al.,* 2015)
Salvianolic Acid B	*Salvia militiorrhiza* root	↓TC, ↓TG, ↓LDL, ↓FA, ↑HDL	Rats	(Qin *et al.,* 2019)
Chrysin	Several honeys, propolis, fruits and vegetables	↓TC, ↓TG, ↓LDL, ↓VLDL, ↑HDL	Mice	(Olas 2020)
Ergosterol	E*dible mushrooms*	↓TG, ↓LDL	Rats	(He *et al.,* 2019)
Ginsenoside-Rd	*Panax* spp.	↓Formation of foam cells	Mice	(Cao *et al.,* 2013)
Ginsenoside-Rg1	*Panax* spp.	↓TC, ↓TG	Mice	(Liu *et al.,* 2018)
Jatrorrizin	*Coptis* spp.	↓TC, ↓TG, ↓LDL, ↑HDL	Mice	(Yang *et al.,* 2016)
Curcumin	*Curcuma longa*	↓TC, ↓TG, ↓LDL	Rats	(Panahi *et al.,* 2018)
Leoligin	*Leontopodium alpinum* root	↓TC, ↓LDL, ↑HDL	Mice	(Scharinger *et al.,* 2016)
Leonurin	*Leonurus japonicus*	↓TC, ↓TG, ↓LDL	Mice	(Suguro *et al.,* 2018)
Lovastatin	*Cantharellus cibarius, Agaricus bisporus*, *Imleria badia*, *Lentinula edodes*	↓TC, ↓LDL, ↑HDL	Rats	(Kała *et al.,* 2020)
Luteolin	*Apium graveolens*, *Piper nigrum*, minyak zaitun, *Thymus vulgaris*, *Origanum vulgare*, *Daucus carota*, *Salvia rosmarinus*	↓TC, ↓TG, ↓LDL	Mice	(Faisal Manzoor *et al.,* 2017)
Monaskin & ankaflavin	*Monascus purpureus*	↓TC, ↓TG, ↓LDL, ↑HDL	Rats	(Lee *et al.,* 2018)

Note : ApoB = Apolipoprotein B; HDL = *High-Density Lipoprotein*;
LDL = *Low-Density Lipoprotein*; NEFA = *Non Esterified Fatty Acid*
TG = Triglyceride; TC = *Total Cholesterol*; VLDL = *Very Low Density Lipoprotein*
↓ = decrease; ↑ = increase

Table 2. Antihypercholesterolemic bioactive compounds with cholesterol absorption inhibitory mechanism

Bioactive compounds	Mechanisms	References
Ergosterol	Inhibits micellar formation	(He *et al.,* 2019)
Luteolin	Inhibit NPC1L1	(Kobayashi 2019)
Palmatin	Inhibit ASBT	(Ning *et al.,* 2015)
β-glucan	Binds bile acids and inhibits micellar formation	(Sima *et al.,* 2018; Korolenko *et al.,* 2020)
Ellagic acid	Inhibit MTTP and ApoB synthesis	(Kubota *et al.,* 2019)
Camphene	Inhibit MTTP	(Vallianou and Hadzopoulou-Cladaras 2016)

Table 3. Antihypercholesterolemic bioactive compounds with cholesterol synthesis inhibitory mechanism

Bioactive compounds	Mechanisms	References
Lovastatin	Inhibit HMG-CoA reductase	(Kała *et al.,* 2020)
Leoligin	Inhibit HMG-CoA reductase	(Scharinger *et al.,* 2016)
Naringin	Inhibit HMG-CoA reductase	(Rotimi *et al.,* 2018)
Ginsenoside Rg1	Inhibit HMG-CoA reductase by AMPK activation	(Liu *et al.,* 2018)
Berberine	AMPK activation	(Pang *et al.,* 2015)
Leonurin	Inhibit SREBP, FAS, SCD1	(Suguro *et al.,* 2018)
Jatrorrizin	Inhibit SREBP1c & FAS	(Yang *et al.,* 2016)
26-oxygenosterol	Inhibit lanosterol 14α-demethylase	(Hajjaj *et al.,* 2015)
Monaskin & ankaflavin	Inhibit MTTP, ACAT, ApoB100 biosynthesis	(Lee *et al.*. 2018)
Ellagic acid	Inhibit MTTP and ApoB synthesis	(Kubota *et al.,* 2019)
Camphene	Inhibit MTTP	(Vallianou and Hadzopoulou-Cladaras 2016)

Table 4. Antihypercholesterolemic bioactive compounds with increase cholesterol excretion mechanism

Bioactive compounds	Mechanisms	References
Curcumin	Increase CYP7A1	(Ghelani *et al.,* 2019)
Gypenocide	Increase CYP7A1, CYP27A1, CYP46A1	(Biswas *et al.,* 2020)

Table 5. Antihypercholesterolemic bioactive compounds with the mechanism of increasing cholesterol efflux

Bioactive compounds	Mechanisms	References
Gypenocide	Increase ABCA1, ABCG1, TSPO	(Biswas *et al.,* 2020)
Ginsenoside-Rd	Increase ABCG1, reduce influx to macrophages by inhibiting SR-A	(Cao *et al.,* 2013)
Icariin	Increase SRB1	(Yang *et al.,* 2015)
Naringin	Increase ApoA1 expression	(Ayoub 2022)
Camphene	Increase ApoA1 expression	(Vallianou and Hadzopoulou-Cladaras 2016)
Monaskin & ankaflavin	Increase ApoA1 expression	(Lee *et al.,* 2018)
Leoligin	Inhibit ECTP	(Scharinger *et al.,* 2016)
Berberine	Nrf2/HO-1 signaling	(Yang *et al.,* 2019)

Table 6. Antihypercholesterolemic bioactive compounds with the mechanism of increasing LDL receptor expression

Bioactive compounds	Mechanisms	References
Monaskin & ankaflavin	Increase LDL receptor	(Lee *et al.,* 2018)
Resveratrol	Increase LDL receptor by SREBP activation	(Rašković *et al.,* 2019)
Hesperetin	Increase LDL receptor by SREBP-1a and SREBP-2 activation	(Bawazeer *et al.,* 2016)
Naringenin	Increase LDL receptor by SREBP-1a and SREBP-2 activation	(Bawazeer *et al.,* 2017)
Ellagic acid	Increase LDL receptor by ERK activation	(Kubota *et al.,* 2019)
Berberine	Increase LDL receptor by ERK & *c-Junk-N-terminal kinase* activation; Increase ApoE expression	(Pang *et al.,* 2015)

Table 7. Antihypercholesterolemic bioactive compounds with the mechanism of increasing fatty acid and cholesterol catabolism

Bioactive compounds	Mechanisms	References
Jatrorrizin	Increase PPAR-α & CPT1A	(Yang *et al.,* 2016)
Eugenol	Increase lipid β-oxidation by TRPV-1 activation; increase UCP-2 by TRVP-1 activation	(Harb *et al.,* 2019; Zhang *et al.,* 2020)

Inhibition of acetyl-CoA carboxylase (ACC) was found in naringenin supplementation. The ACC plays a role in transforming acetyl-CoA into fatty acids. Inhibition of ACC has been shown to decrease lipogenesis and increase fatty acid oxidation (Kim *et al.,* 2017). In addition, naringenin and jatrorrizin inhibit the activity of fatty acid synthase (FAS), an enzyme that catalyzes the final stage of the fatty acid biosynthesis process (Yang *et al.,* 2016).

Sterol regulatory element-binding protein (SREBP) is a group of transcription factors that regulate gene expression in cholesterol and fatty acid biosynthesis. Members of this group consist of SREBP-1a, SREBP-1c, and SREBP-2 (Rong *et al.,* 2017). Complex activation of SREBP causes the activation of various enzymes involved in the synthesis of cholesterol, fatty acids, triacylglycerols, and phospholipids (Bertolio *et al.,* 2019). Leonurin inhibition of the SREBP complex leads to a decrease in genes expressing FAS and stearoyl-coenzyme A desaturase 1 (SCD1) which are involved in lipogenesis (Suguro *et al.,* 2018). Various bioactive components target inhibition of SREBP-1c specifically, such as those found in allicin, tetramethylpyrazine, ursolic acid, jatrorrizin, and naringenin. (-)-epicatechin inhibits SREBP via the Insig-1-SREBP-SCAP signalling pathway. The SREBP cleavage-activating protein (SCAP) and insulin induced-gene (Insig) are both detectors and regulators that maintain cholesterol homeostasis by binding to each other. The bond formation is induced by hypercholesterolemic conditions that can inactivate SREBP to suppress the expression of the HMG-CoA reductase gene (Nakano *et al.,* 2022).

Microsomal triglyceride transfer protein (MTTP), a protein that is a factor in the production of ApoB100, was not only found in the endoplasmic reticulum of enterocytes but also in hepatocytes. The MTTP inhibition is the work target of the bioactive components of camfena, ellagic acid and monaskin and ankaflavins. As a precursor to atherogenic lipoproteins, ApoB100 is a target for monaxin and ankaflavin by inhibiting their excessive expression and secretion from the liver (Lee *et al.,* 2018).

Increased Cholesterol Excretion

Bile acid metabolism is part of the mechanism of cholesterol homeostasis. The secretion of bile acids mediates the excretion of cholesterol, the only significant pathway for the elimination of cholesterol from the body. Secreted bile acids play a role in the emulsification of lipids in food and in digestive tract. Most of the bile acids (95%) will be returned to the body via the enterohepatic reabsorption pathway while the rest will be excreted along with the faeces (Durník *et al.*, 2022). Bile acid biosynthesis involves cholesterol conversion which is initiated by cholesterol 7α-hydroxylase (CYP7A1) and controlled by the gene of the same name (Chiang and Ferrell, 2021). Cholesterol 7α-hydroxylase (CYP7A1) is a limiting enzyme in cholesterol biosynthesis. All antihypercholesterolemic bioactive components that affect cholesterol excretion act by increasing CYP7A1 expression (Table 4). Variations were found in the bioactive component of gypenoside which also led to increased expression of CYP27A1 and CYP46A1, which play a role in cholesterol metabolism and bile acid biosynthesis (Biswas *et al.,* 2020).

Increased Cholesterol Reverse Transport

Reverse transport of cholesterol is the process of removing cholesterol from tissue cells and macrophage foam cells through lipoprotein intermediates to be degraded in the liver and excreted through bile acids. The reverse transport intermediate lipoprotein is HDL. Reverse transport includes the cholesterol efflux process, the stages of cholesterol transfer from cells to HDL (Ouimet *et al.,* 2019). The cholesterol efflux process can be in the form of cholesterol transfer from cells to the pre-β HDL subfraction, Apo-A1 particles which are low in cholesterol content. This efflux process is mediated by ATP-binding cassette transporter A1 (ABCA1) on the cell membrane surface. Another mechanism of cholesterol efflux involves the transfer of cholesterol from cells to mature HDL particles through the ATP-binding cassette transporter G1 (ABCG1). Both mechanisms are processes of cholesterol efflux that occur actively. Cholesterol efflux can also occur passively by transferring cholesterol from cell membranes to HDL particles through passive diffusion (Getz and Reardon, 2018). Cholesterol captured by HDL particles will undergo esterification. Cholesterol esters stored in HDL are then further transferred through two alternative mechanisms. First, HDL particles will collect cholesterol to the liver via the scavenger receptor class B type 1 (SR-B1). The second

mechanism is the transfer of cholesterol from HDL to low-density lipoprotein particles such as LDL and VLDL which will then be taken up by the liver through LDL receptors (Maranhão *et al.,* 2018). Based on this mechanism, the antihypercholesterolemic bioactive compounds can be categorized according to their mechanism by increasing cholesterol efflux (Table 5) and increasing LDL receptor expression (Table 6).

Increased Cholesterol Efflux.

Some of the bioactive components that work in the cholesterol efflux mechanism show an effect on increasing the ATP-binding cassette subfamily (ABCs), ABCA1 and ABCG1. Both components play an important role in the efflux of cholesterol from macrophages to HDL particles. Several bioactive components showed increased ABC expression through activation of PPAR-γ, a transcriptional regulator of ABC (Trapnell and Luisetti, 2020). PPAR-γ increases ABC expression through induction of liver X receptor (LXRα). Activation of LXRα will stimulate efflux and cholesterol transport. The overall mechanism forms the PPAR-γ-LXRα-ABC signalling pathway.

Scavenger receptor B1 (SR-B1) is a functional receptor that not only acts as an acceptor of cholesterol influx from HDL in the liver but also as a mediator of cholesterol efflux from tissue cells and macrophages (Shen *et al.,* 2018). Increased expression of SR-B1 is the target of action of the bioactive component of icariin (Yang *et al.,* 2015). Increased cholesterol efflux from macrophages was also found in gypenoside supplementation. Gypenoside increases cholesterol efflux by increasing the activation of translocator protein (TSPO) (Biswas *et al.,* 2018). A different mechanism is shown by the bioactive tanshinone IIA and ginsenoside-Rd which suppress cholesterol influx into macrophages by inhibiting the expression of scavenger receptor A (SR-A). SR-A acts as a mediator of the influx of oxidized LDL by macrophages, a cause of foam cell formation and a risk factor for the development of atherosclerosis (Mineo 2021).

Increased secretion of apolipoprotein A-I (apoA-I) occurred with supplementation of naringin (Ayoub 2022), camphene (Vallianou and Hadzopoulou-Cladaras, 2016), monaskin and ankaflavin (Lee *et al.,* 2018). ApoA-I is the precursor as well as the main constituent fraction of HDL particles. Increased apoA-I secretion was positively correlated with increased serum HDL levels and cholesterol reverse transport rates (Valanti *et al.,* 2018). An increase in the cholesterol efflux also demonstrated in berberine supplementation. Berberine can regulate cholesterol efflux via Nrf2/HO-1 signaling in ApoE$^{-/-}$ mice, thus, suppresses foam cells formation (Yang *et al.,* 2019).

Several bioactive components support the reverse transport of cholesterol by HDL by inhibiting cholesteryl ester transfer protein (ECTP). ECTP is an enzyme that mediates the transfer of cholesterol and triglyceride esters from HDL to low-density lipoproteins such as LDL and VLDL. The low expression of ECTP supports the increased formation of HDL thereby promoting an increase in cholesterol reverse transport. High levels of ECTP can support reverse cholesterol transport as long as it is accompanied by high LDL receptor expression (Inazu 2017). Effective reverse transport of cholesterol through HDL makes efforts to increase serum HDL levels one of the main strategies for treating hypercholesterolemia. Inhibition of ECTP was found in the bioactive compounds of anthocyanins (Tian *et al.,* 2016) and leoligin (Scharinger *et al.,* 2016).

Increased Expression of LDL Receptors

Most of the bioactive compounds that act on the cholesterol reverse transport mechanism increase the expression of LDL receptors in the liver. The LDL receptor expression is regulated at the molecular level by sterol regulatory binding protein (SREBP). The SREBP is a family of transcription factors that directly control more than 30 genes involved in the biosynthesis and transport of cholesterol and fatty acids. Genes that play a role in LDL receptor expression are also controlled by SREBP. The major SREBP members identified were SREBP-1a, SREBP-1c, and SREBP-2 (Robinet and Smith, 2015). The results of the study on HepG2 cells showed that LDL receptor expression was mainly controlled by SREBP-1a and SREBP-2 (Bawazeer *et al.,* 2017). This is found in the antihypercholesterolemic activity of hesperetin (Bawazeer *et al.,* 2016). The SREBP activation is also shown by the action of the bioactive component resveratrol which contributes to an increase in LDL receptors (Rašković *et al.,* 2019).

Variations of activation pathways that play a role in increasing LDL receptor expression were found in the bioactive components of ellagic acid (Kubota *et al.,* 2019) and berberine

(Pang *et al.,* 2015). Both of these bioactive components work through pathways regulated by an extracellular signal-regulated kinase (ERK). The ERK pathway increases LDL receptor expression through increased mRNA stabilization. Berberine has an additional activation pathway that also involves a c-Junk N-terminal kinase-mediated pathway that plays a role in increasing the transcriptional activity of LDL receptors (Pang *et al.,* 2015).

Increased Cholesterol Catabolism

Efforts to overcome hypercholesterolemia can be taken by increasing the catabolism of cholesterol and fatty acids in the body. Various bioactive components with these targets are shown in Table 7. Increased lipid metabolism contributes to a decrease in tissue lipid accumulation and various serum lipid fractions which are risk factors for hypercholesterolemia (Badimon and Chiva-Blanch, 2019). Activation of PPAR and transient receptor potential vanilloid (TRPV1) in the liver has been shown to increase energy use by increasing lipid oxidation (Harb *et al.,* 2019). The induction of lipid metabolism by PPAR activation is mediated by uncoupling protein 2 (UCP2). Studies in mice have shown that activation of UCP2 in the liver contributes to an increase in the rate of -oxidation of fat and a decrease in triglyceride and tissue fat levels (Zhang *et al.,* 2020). The increase in the rate of fat metabolism involves both PPAR-α and PPAR-γ. PPAR-α dominantly plays a role in regulating the chain of β-oxidation reactions of fat (Pawlak *et al.,* 2015) while PPAR-γ regulates the storage and use of fat reserves (Crossland *et al.,* 2021). Jatrorrizin supplementation led to increased expression of PPAR-α which induces activation of carnitine palmitoyltransferase 1A (CPT1A), a gene involved in the oxidation of fatty acids in mitochondria (Yang *et al.,* 2016). Variations are shown by the action of capsaicin by increasing sympathetic nerve stimulation which induces an increase in the rate of fat catabolism through noradrenaline secretion (Aydin 2015).

CONCLUSION

Natural antihypercholesterolemic bioactive compounds became an alternative treatment for the hypercholesterolemic condition. The bioactive compounds showed various sources, efficacy, and mechanism of action. Various antihypercholesterolemic bioactive compounds can be classified according to their mechanism, namely inhibiting cholesterol absorption and cholesterol biosynthesis; and increasing cholesterol excretion, cholesterol reverse transport, and cholesterol catabolism. Through understanding these mechanisms, alternative medicine and hypercholesterolemia treatment strategies may be developed.

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