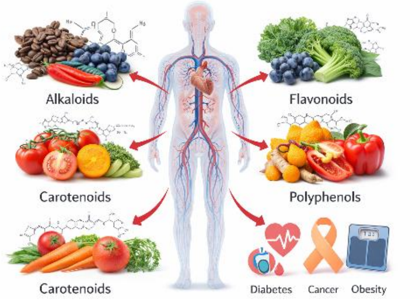

CHAPTER 19

Natural Compounds in Metabolic Disorders: Diabetes, Obesity and Cardiovascular Diseases

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ABSTRACT: This chapter provides an overview of research into the efficacy of natural substances for the management of obesity, diabetes, and cardiovascular diseases (CVDs). The pathogenesis of these disorders is almost similar and includes oxidative damage, inflammation, and insulin resistance. The study claims that alkaloids and polyphenols, two anti-diabetic substances, boost insulin activity while preserving blood glucose stability. Moreover, the current chapter examines the impact of anti-obesity drugs on gut flora and lipid metabolism, with a focus on flavonoids and diets high in fiber. Furthermore, this chapter assesses the cardioprotective advantages of carotenoids and polyphenols by looking at their anti-inflammatory and antioxidant properties. Additionally, a summary of clinical trials, present barriers to bioavailability improvement and standardization are also provided. Moreover, this chapter proposes future directions for the application of natural compounds in personalized medical care.

A wide range of illnesses resulting from abnormalities in biological metabolic processes are referred to as metabolic disorders. What causes the ailment is the primary emphasis of the categorization system. Based on whether they are acquired or inherited, metabolic diseases are divided into two categories by medical specialists. Genetic abnormalities that impact the function of particular metabolic pathways are the root cause of hereditary metabolic illnesses. These incredibly uncommon diseases include mucopolysaccharidoses, Gaucher disease, and phenylketonuria.

Most metabolic disorders that manifest after birth are much more common and result from a combination of genetic and environmental factors. Because they encompass common ailments like diabetes, osteoporosis, and obesity, people are exposed to these disorders on a regular basis. The prevalence of several diseases has dramatically increased during the past few decades, making them important public health concerns. Medical authorities estimate that approximately 33% of individuals worldwide are overweight or obese (Chooi et al., 2019).

Insulin resistance and diabetes both independently raise the death rate among heart failure patients and are powerful indicators of the development of cardiovascular disease. Diabetes damages heart and blood artery tissue, but the complex molecular pathways behind these consequences are poorly understood. Diabetes-

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related cardiovascular problems are caused by a variety of circumstances. Atherosclerotic disease often affects many bodies vascular areas. Hypertension is a prevalent health problem for most people with diabetes. In addition to dyslipidaemia and hyperglycaemia, the proinflammatory condition associated with obesity results in long-term increases in systemic adrenergic activity. While in circulation, several bioactive compounds exhibit aberrant concentration levels(Scherer & Hill, 2016).

Throughout human history, natural products have been a vital source of therapeutic agents, and they still make up a sizable amount of modern medications (Atanasov et al., 2015). Natural substances that have a significant importance include luteolin, curcumin, cinnamon aldehyde, berberine, and anthocyanins. Berberine increases insulin sensitivity, increases the energy expenditure of fat cells, and decreases blood lipid levels as well as fat synthesis via activating AMPK (Rochlani et al., 2017) According to preclinical studies, in animal models, berberine, curcumin (found in turmeric), and cinnamon aldehyde (found in cinnamon) improve insulin signalling, prevent weight gain, decrease the formation of fat cells, and improve blood sugar management (Urasaki & Le, 2022).

The current chapter discusses the medical usefulness of natural compounds for treating metabolic disorders that include diabetes, cardiovascular diseases and obesity. Moreover, the chapter describes the therapeutic actions of plant molecules which include polyphenols, flavonoids and alkaloids, that influence important metabolic functions. Recent preclinical and clinical studies along with safety profiles and action mechanisms are also analyzed. Current research limitations and future research directions for natural therapeutics in metabolic health are also studied.

PATHOPHYSIOLOGY OF METABOLIC DISORDERS

Overweight, non-diabetic people (including Pima Indians) are observed to have increased insulin production to compensate for insulin resistance, which helps them maintain normal blood glucose levels (retain proper insulin resistance compensation). However, this compensation is only effective in the absence of a β-cell defect. Type 2 diabetes is associated with elevated blood sugar levels while fasting and after meals, which are caused by a decline in β-cell activity. Several extrinsic variables, including the availability of sugar, inactivity, and weight gain, as well as the negative consequences of high blood glucose, free fatty acids, and insulin resistance, can cause β-cell degradation. Insulin resistance may worsen when free fatty acids are combined with resisting and tumour necrosis factor-alpha (TNF-α). By appropriately reestablishing metabolic regulation, the β-cell dysfunction brought on by glucose toxicity and lipo-toxicity may be resolved (LeRoith, 2002).

When food consumption surpasses energy intake, an excessive buildup of adipose tissue occurs, leading to obesity. According to recent research, adipose tissue serves as both an endocrine organ and a reservoir of excess energy from food consumption. As adipose tissue forms, a variety of bioactive compounds known as adipocytokines or adipokines are created. These chemicals cause chronic low-grade inflammation and affect several organ systems. Although the precise processes are yet to be understood, excess and damaged adipose tissue produces adipokines in aberrant ways that contribute to the development of metabolic issues associated with obesity (Jung & Choi, 2014).

The primary factor that causes cardiovascular issues is atherosclerosis. The vascular branching sites of the intima layer are where middle to large sized arteries are the most susceptible to atherosclerosis. This phenomenon can be explained by the features of blood flow patterns, since areas that experience normal shear stress are resistant to atherosclerosis. Atherosclerosis causes stenosis and atherothrombosis, which limit blood flow and cause cardiovascular disease. By thickening the arterial wall and damaging the arterial tree, hypertension increases the chance of plaque rupture (Poznyak et al., 2022). Endothelial dysfunction brought on by aging, menopause, and high cholesterol leads to the development of atherosclerotic vascular lesions and the susceptibility of blood arteries to several vascular disorders, such as thrombosis and vasospasm. Endothelial dysfunction associated with atherosclerosis seems to be caused via a variety of intricate mechanisms. Endothelial nitric oxide synthase cofactor availability, L-arginine supply, enzyme expression and disruptions in endothelial signal transmission all contribute to decreased endothelial nitric oxide synthesis (Shimokawa, 1999). The incidence of cardiac events is directly and significantly correlated with endothelial dysfunction. Endothelial dysfunction is necessary for atherosclerosis and probably plays a role in the development of blood clots later in the illness (Jay Widmer et al., 2014).

The primary causes of diabetes, obesity, and cardiovascular diseases are oxidative stress and mitochondrial dysfunction. Excessive reactive oxygen species generation disrupts insulin signaling and results in chronic inflammation, which worsens energy regulation and quickens metabolic deterioration (Bhatti et al., 2017).

ANTI-DIABETIC NATURAL COMPOUNDS

Polyphenols

Plant-based foods, including tea, soy, coffee, chocolate, cereal grains, cinnamon, ginger, fruits, and berries include a broad family of phytochemicals called polyphenols. Anthocyanins, flavonols, flavones, flavanones, isoflavones, and flavonoids are among the many types of polyphenols that may be found in nature. Flavonoids are one of the best types of polyphenols that people usually consume. This molecule is composed of a heterocyclic ring with oxygen that is formed by joining two phenolic rings with three carbon atoms (Sun et al., 2020).

Plant-based polyphenolic compounds, such as resveratrol, curcumin, and quercetin, are naturally occurring chemicals that improve cellular glucose absorption, protect pancreatic β-cells, activate AMPK pathways, and improve insulin sensitivity. Resveratrol improves insulin sensitivity in the human body by significantly reducing HOMA-IR and oxidative stress markers and increasing Akt phosphorylation in the insulin-signaling pathway (Wong & Howe, 2018). Prolonged resveratrol intake causes AMPK activation, which lowers blood glucose levels and hepatic gluconeogenesis. Furthermore, research using diabetic animal models has demonstrated that it improves skeletal muscle GLUT4 expression, pancreatic insulin protein, and β-cell mass preservation (Do et al., 2012). Resveratrol protects the pancreatic islets against oxidative damage, fibrosis, and β-cell death, preserving their ability to secrete insulin (Lee et al., 2012). Fig. 1 demonstrates the chemical structure of resveratrol.

Curcumin (Fig. 2) improves pancreatic β-cell survival and insulin production *in vitro*. When exposed to glucose, both humans and animals who received dosages of curcumin released more insulin. At the same time, apoptosis was decreased by the

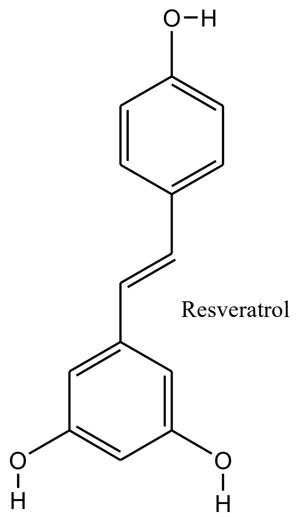


Fig. 1. Resveratrol chemical structure

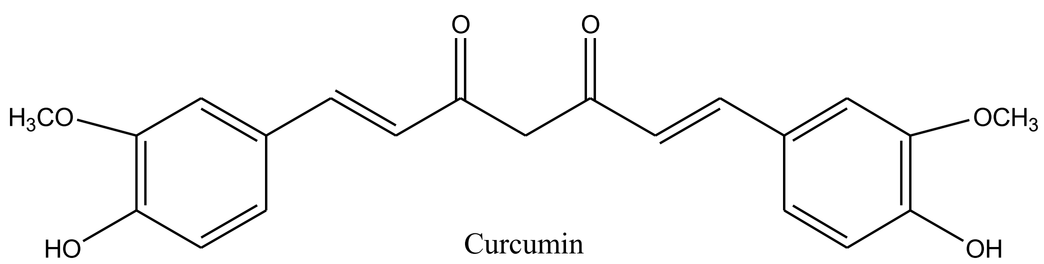


Fig 2. Chemical structure of Curcumin

modulation of the ERK1/2 and PCG-1α pathways. Moreover, it also increased PI3K/Akt signaling, GLUT2 expressions, while ROS levels as well as inflammatory signals, such as NF-κB and ER stress indicators and CHOP decreased (Hartogh et al., 2020). After taking curcumin supplements for a year, obese individuals with type 2 diabetes showed a notable increase in β-cell activity and lowered insulin resistance. Furthermore, their fasting glucose and HbA1c values dropped (Yaikwawong et al., 2024).

Furthermore, quercetin (Fig. 3) also showed anti-diabetic effects via activating the AMPK pathway and increasing the absorption of glucose. Meanwhile, it decreased the synthesis of glucose in the liver via inhibiting gluconeogenic enzymes and triggering PI3K / Akt-dependent GLUT4 translocation in liver, muscles, and adipose cells. Reportedly, quercetin protected against oxidative and cytokine-induced damage as well as promoted islet survival and regeneration. It also stimulated calcium influx through L-type channels and glucose-stimulated insulin production in mice pancreatic β-cells. Research on streptozotocin induced diabetes in animals showed that quercetin improved lipid profiles, lowered blood sugar, and promoted β-cell regeneration (Li et al., 2019).

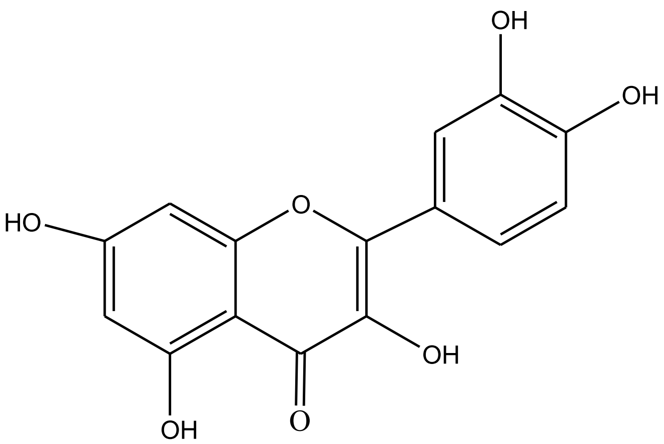
Alkaloids

Alkaloids is a significant family of nitrogen-containing compounds with a wide range of biological and therapeutic applications. These substances are found in a variety of plants as well as animals, such as marine life, vertebrates, and certain fungi (Rasouli et al., 2020).

Coptis chinensis and Berberis species naturally contain berberine, an isoquinoline alkaloid that suppresses hepatic gluconeogenesis and activates AMPK pathways. Reportedly, berberine increases TORC2 phosphorylation and cytoplasmic retention via inhibiting PEPCK and G6Pase gluconeogenic enzymes through the induction of LKB1-AMPK signaling (Jiang et al., 2015). According to research, berberine reduces hepatic gluconeogenesis through both AMPK-dependent and AMPK-independent routes by inhibiting SIRT3, which causes mitochondrial malfunction, and increases AMP/ATP ratio, which activates AMPK (Zhang et al., 2018). Because AMPKα1 is absent in HepG2 cells, berberine cannot increase glucose absorption while decreasing glucose synthesis, suggesting that AMPK is an essential mediator for berberine's metabolic effects (Ren et al., 2020). Moreover, berberine produced more hypoglycemic effects when it was combined with traditional anti-diabetic drugs (Liang et al., 2019). Fig. 4 shows the chemical structure of berberine.

Other Plant-Derived Agents

The plants, *Schisandra chinensis*, *Potentilla discolor Bunge*, *Eriobotrya japonica*, *Weigela subsessilis*, and *Lagerstroemia speciosa* L., contain the ursane-type triterpenoid called corosolic acid, otherwise known as 2α-hydroxyursolic acid (Park, 2019). Current research has focused on identifying and creating structural glycogen phosphorylase (GP) inhibitors since the discovery of GP's natural inhibitory function through corosolic acid. The first double-blind human study investigating the



Quercetin

Fig 3. Chemical structure of Quercetin

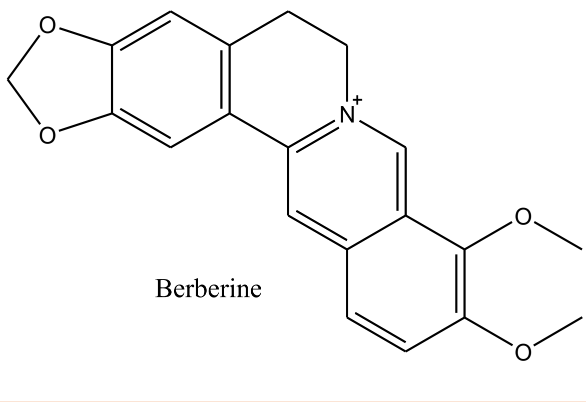


Fig 4. Berberine chemical structure

antidiabetic effects of corosolic acid was conducted by Fukushima et al., (2006). Researchers are investigating corosolic exhibits as a possible superior anti-diabetic drug due to its mild hypoglycaemic effects in human clinical studies. In addition to corosolic acid, gymnemic acid also exhibits anti-diabetic properties. The following routes mediate hypoglycemic effects of gymnemic acid:

1. It encourages the production of more insulin.
2. It promotes the renewal of islet cells.
3. It enhances glucose utilization by reducing the activity of sorbitol dehydrogenase and gluconeogenic enzymes, as well as by raising the activity of phosphorylases and insulin-dependent glucose consumption enzymes.
4. It prevents glucose from being absorbed by the digestive tract. Gymnemic acid binds to intestinal receptors and stops glucose molecules from binding to them, reducing excessive glucose absorption (Laha & Paul, 2019).

ANTI-OBESITY COMPOUNDS AND MECHANISMS

An imbalance between energy expenditure and calorie intake, preferring higher intake over expenditure, is caused by a combination of genetic, psychological, and socioenvironmental factors that result in the accumulation of extra body fat, which is the medical condition known as obesity (Jimoh, 2016). Various plant-derived compounds exhibit anti-obesity properties. Some of those are discussed here.

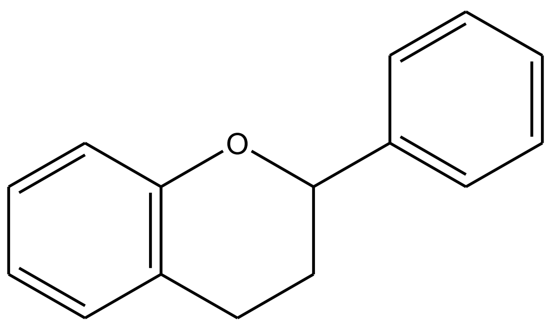
Flavonoids

Flavonoids possess significant anti-obesity properties. These are polyphenolic compounds, and their structural formula is presented in Fig. 5. Naringenin is a plant-based flavonoid, and its supplementation is reported to raise the expression of Pnpla 2, Pgc1-α, and Cpt1-α genes in the liver via encouraging fatty acid uptake and oxidation. Through this mechanism, naringenin protects from hepatic steatosis by inhibiting the formation of atheromatous plaque and lipid buildup in hepatocytes. Burke et al. (2018) reported that naringenin successfully regulated weight gain, reduced insulin resistance and dyslipidemia which consequently lowered atherosclerosis in mice with a high-fat, high-cholesterol diet. Naringin caused AMPK phosphorylation, which decreased PCSK9 production, LDLR degradation and prevented SREBP cleavage as well as transcriptional activation. Sui et al., (2018) found that the therapy decreased body mass and fat formation in mice fed a high-fat diet. Naringenin has demonstrated potential in enhancing the body's reaction to glucose and controlling insulin as well as blood sugar levels.

In addition to naringenin, epigallocatechin gallate also lowers obesity. By lowering blood free fatty acid levels, increasing insulin pathway proteins PI3K and GLUT4, and lowering IRS1 (Insulin Receptor Substrate 1) serine phosphorylation, a meal rich in epigallocatechin gallate improved glucose absorption and restored insulin action sensitivity in adipose tissue (Bao et al., 2014). Epigallocatechin-3-gallate, epicatechin, apigenin, quercetin, myricetin, and cyanidin 3-glycoside were found to decrease MCP-1, an important adipocytokine that regulates monocyte / macrophage migration and infiltration (Ke et al., 2011). Cremonini et al. (2018) found that giving (-) epicatechin reduced insulin resistance and hepatic inflammation brought on by a high-fat diet. It also reduced NOS2 synthesis, the F4/80 macrophage marker, and endotoxemia (Cremonini et al., 2018).

Terpenoids and Essential Oils

Essential oils and terpenoids possess anti-obesity potential. Essential oils regulate energy metabolism by controlling lipolysis and lipogenesis through appetite modulation. The volatile chemicals in essential oils engage certain olfactory receptors,



Flavonoids

Fig 5. General structures of Flavonoids which in turn cause central nervous system (CNS) responses (Shen et al., 2005). There are several uses for oregano-derived essential oils in the culinary, cosmetic, and medical fields. Terpenes in essential oils of oregano, consists of both monoterpenes and sesquiterpenes, are responsible for their biological effectiveness (Leyva-López et al., 2017). Oregano, particularly the type with the highest content of carvacrol, has anti-obesity qualities. Carvacrol has been demonstrated to reduce lipid accumulation during adipogenic development in murine 3T3-L1 cell lines and human Wharton's gelatin-derived mesenchymal stem cells. The transcription factor ChREBP (Carbohydrate Response Element-Binding Protein) regulates adipogenesis and changes in it are the major reasons that reduce adipogenic differentiation (Spalletta et al., 2018).

Phytochemicals contain the most extensive family of terpenoids, which function as light-harvesting pigments, hormones, phytoalexins and semi-chemicals. These compounds exhibit their therapeutic function mostly due to their universal five-carbon building blocks (Singh et al., 2022). Ginsenosides (Fig. 6) and cucurbitane-type triterpenoids can reduce fat accumulation by improving glucose absorption through GLUT4, even in the absence of insulin by increasing insulin receptor activation. 24-Methylenecycloartan-3-one helps in reducing metabolic stress by safely lowering blood sugar levels. The α-amylase and α-glucosidase enzymes are inhibited by sage essential oils; these oils lower calorie intake and hinder the breakdown of carbohydrates. In animal models that were given high-fat diets, oleanolic acid has been demonstrated to reduce body weight and fat mass. Through PPARγ pathways and mitochondrial antioxidant signals, it also enhances inflammatory control, liver fat reduction, and insulin resistance (Zhang et al., 2024). By focusing on insulin signaling, oxidative stress, lipid metabolism, glucose absorption, and digestive enzyme function, these natural substances work together to promote weight control and metabolic health (Singh et al., 2022).

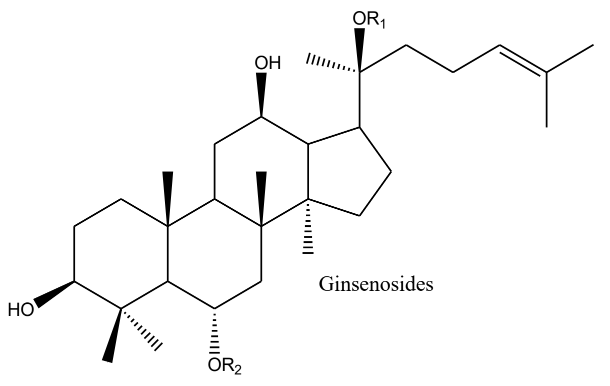


Fig. 6. Ginsenosides

Fiber-Rich and Functional Foods

Fiber-rich foods are also beneficial against obesity. Because they alter metabolic processes and the makeup of the gut flora, dietary interventions that incorporate soluble fiber, resistant starch, and plant sterols are helpful in the battle against obesity. According to Li et al. (2024), the soluble fibers β-glucans and psyllium form gels inside the gut that bind bile acids, slow stomach emptying and reduce cholesterol absorption. This improves satiety, regulates blood sugar response, and decreases LDL cholesterol. These benefits enhance metabolic indicators and lower caloric consumption.

The resistant starch, found in whole grains, legumes, and cold potatoes, is fermented by the gut flora in the colon and is not digested in the small intestine. Butyrate is a primary short-chain fatty acid that is produced by fermenting resistant starch, reduces inflammation, increases insulin sensitivity, and prevents the accumulation of fat (Vahdat et al., 2020). In overweight and obese individuals, eight weeks of RS supplementation led to 2.8 kg of weight reduction, improved glucose tolerance, and decreased systemic inflammation. Positive bile acid profiles and elevated *Bifidobacterium adolescentis* levels were associated with these results (Li et al., 2024).

The combination of plant sterols, stigmasterol and β-sitosterol found in nuts, seeds, fruits, vegetables and whole grains also lowers LDL cholesterol via blocking the absorption of cholesterol from the diet. According to a recent study, plant sterols have an impact on the gut microbiota, which includes enhancement of the integrity of the intestinal barrier, as well as the lowering of dangerous bacterial populations and chronic inflammation, which are linked to obesity (Vezza et al., 2020).

CARDIOPROTECTIVE EFFECTS OF POLYPHENOLS AND CAROTENOIDS

The main cause of death worldwide at the moment is cardiovascular diseases. Research indicates that hypertension, which accounts for 39.4% of cases, is the main risk factor for CVD. The second largest risk factor is being overweight, at 34.1%, which is followed by smoking (23.6%) and hypercholesterolemia (18.7%) (Das et al., 2022).

Polyphenols

Polyphenols exhibit significant cardioprotective effects. Adequate synthesis and bioavailability of nitric oxide (NO) are essential for maintaining vascular homeostasis. Nitric oxide is essential to the basic process that regulates vascular tone. O^{2-} radicals mostly damage NO molecules. However, flavonoids with antioxidant qualities remove and lower the levels of free radicals as well as boost the availability of NO. Due to these reasons, polyphenols may have positive effects on the circulatory system. Polyphenols may have a vasodilatory effect through a variety of biological routes (Wallerath et al., 2002; Mattagajasingh et al., 2007). It has been found that red wine polyphenols, such as quercetin and delphinidin, cause endothelium-dependent relaxation in the mesenteric arteries and rat aorta rings (Duarte et al., 2004). By inhibiting endoplasmic reticulum Ca^{++}-ATPase and activating K^{+} channels, resveratrol and quercetin raise intracellular calcium in endothelial cells (Martin & Andriantsitohaina, 2002). Red wine contains the anthocyanin delphinidin, which stimulates endothelial cells and increases intracellular calcium levels. The ability of flavonoids to promote endothelial NO production and cGMP increase in vascular smooth muscle is the main cause of their vasodilator actions (Botden et al., 2011). The general structure of anthocyanins is shown in Fig. 7.

Enzymes including cyclooxygenase (COX) and lipoxygenase (LPO), which facilitate the release of interleukins and chemokines, are produced in greater quantities under oxidative stress. Studies have demonstrated that polyphenols, particularly flavonoids, inhibit the actions of LPO and COX (Ghafoor et al., 2024; Ahmed et al., 2025; Javed et al., 2025). An anti-inflammatory substance called resveratrol prevents prostaglandin synthesis (Ridker et al., 2004). The anti-inflammatory properties of cocoa's polyphenols can help control inflammatory molecules in those who are more prone to cardiac disease (Abe et al., 2011).

Carotenoids

Carotenoids exhibit antioxidant potential due to their chemical properties and capacity to interact with cellular membranes. β-carotene, lycopene, lutein, β-cryptoxanthin, zeaxanthin, and astaxanthin are the most common dietary carotenoids found in food (Riccioni, 2009). Lycopene is the main carotenoid found in human plasma. Regarding lycopene's capacity to prevent atherosclerosis, researchers have formulated two primary hypotheses: oxidative and non-oxidative processes. One of the non-oxidative methods is to regulate gap-junction communication, which is demonstrated in mouse embryonic fibroblast cells. According to the oxidative hypothesis, preventing LDL oxidation is the first step in the production of foam cells and macrophage uptake, which results in the development of atherosclerotic plaque (Witztum, 1994). According to Witztum (1993), the oxidative changes signify the oxidative degradation of apolipoprotein B and the breakdown of cholesterol, polyunsaturated fatty acids and phospholipids. Eating a variety of fruits and vegetables lowers the incidence of coronary heart disease. Carotenoids, including lycopene, are the main healthy ingredients in fruits and vegetables. Lycopene and other carotenoids, together with a diet rich in tomatoes

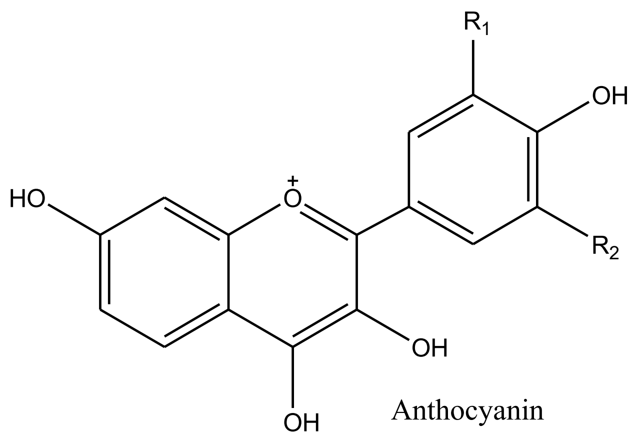


Fig. 7. Chemical structure of Anthocyanin

and tomato-based products, have been shown to help reduce coronary heart disease (Fuhrman et al., 1997).

Synergistic Effects and Dietary Patterns

The DASH and Mediterranean dietary patterns offer substantial cardioprotective and anti-obesity benefits by emphasizing the synergy of whole meals rather than isolated components. Fiber, polyphenols, and omega-3 fatty acids are examples of natural bioactive compounds included in the Mediterranean diet that combine to improve lipid profiles, reduce inflammation, and help control weight (Blanco et al., 2018). By emphasizing low-sodium dairy and lean meats with high potassium consumption, the DASH diet which was first created as a blood pressure treatment strategy has shown promise in reducing body weight and improving metabolic markers. As a result of their combined effects on gut microbial activity, oxidative stress reduction, and appetite regulation, whole-food methods that include numerous nutrients and bioactive compounds work better than supplementing with a single molecule. This illustrates how effective food patterns are at controlling obesity and associated comorbidities (Monzón et al., 2001).

CLINICAL EVIDENCE AND THERAPEUTIC INTEGRATION

Natural substances including berberine, curcumin, resveratrol and silymarin offer potential advantages in the treatment of diabetes and cardiometabolic diseases. These plant-based chemicals have been studied in human clinical trials to see if they can help regulate inflammation, lipid metabolism, and blood sugar.

One of the most studied antidiabetic compounds is berberine. Berberine at doses of 1,000–1,500 mg/day effectively decreased HbA1c levels along with fasting blood glucose, postprandial glucose and triglycerides, and LDL cholesterol levels in patients with type 2 diabetes (Aryaeian et al., 2017). Berberine improves insulin sensitivity and reduces inflammation in people with HIV and metabolic syndrome (Ruiz-Herrera et al., 2023).

People with diabetes and obesity may benefit from curcumin, the main ingredient in turmeric. After taking 300 mg daily for three months, patients' fasting glucose levels, insulin resistance markers, BMI, and HbA1c levels showed significant reductions. The medication reduced free fatty acid levels in the blood without causing any noticeable negative effects (Kambale et al., 2022). Reportedly, silymarin improves liver protection and insulin sensitivity. According to a study, silymarin supplementation reduced fasting glucose levels and liver enzyme levels (Shi et al., 2019).

Product-specific variations in supplement quality and bioavailability make dosage standardization challenging. At daily dosages of 1,000-1,500 mg, berberine has good patient tolerance; nevertheless, it may interfere with medications that are metabolized by CYP3A4, such as cyclosporine and statins. At dosages up to 8 g daily, curcumin's inherent poor bioavailability does not affect its safety profile; nonetheless, researchers must create alternative delivery vehicles, such as nanoparticles or micelles, to enhance absorption. While silymarin is safe to use at daily dosages between 140 and 210 mg, it lacks enough long-term safety proof. Resveratrol's bioavailability varies from person to person and generates dose-dependent adverse responses, which limit its usage in medicine.

CHALLENGES AND FUTURE DIRECTIONS

Despite promising outcomes in the treatment of diabetes and cardiometabolic diseases, several barriers limit the practical use of natural substances. Researchers are currently looking into nanoparticle, liposome, and micelle delivery systems to increase the stability and absorption rates of curcumin, resveratrol, and silymarin because of their poor bioavailability and unstable metabolisms, which cause them to be rapidly broken down and eliminated from the body, leaving minimal systemic concentrations after oral intake (Althouse et al., 2020). It is challenging to standardize dosages and get similar treatment outcomes because of the influence of geographic location, cultivation methods, harvest times, and extraction techniques on the concentration of active chemicals in plant sources (Shu et al., 2022). Many nutraceuticals and phytopharmaceuticals face challenges in extensive safety and effectiveness research and quality control due to their classification as dietary supplements rather than medications, along with a lack of harmonized global regulatory standards (Bennani et al., 2022). To assess the prolonged safety profile, effectiveness, pharmacokinetics, and drug-nutrient interactions across various demographic groups, a large number of clinical trials at various locations are needed. Since modern technologies allow for gut microbiota characterization, genetic and metabolomic analysis, and tailored treatment plans that optimize effectiveness and minimize side effects, the future of personalized nutrition and phytomedicine is bright. Microbial profiles may aid in identifying certain supplementation strategies because the metabolic and bioavailable properties of polyphenols rely on the patterns of each person's gut microbiota (Wang et al., 2022). Before natural agents can successfully treat metabolic illnesses, scientists must overcome manufacturing, regulatory and scientific obstacles.

CONCLUSION

Natural chemicals provide a potential strategy for the prevention and treatment of metabolic illnesses, such as diabetes, obesity, and cardiovascular disease. Preclinical and clinical studies have demonstrated that polyphenols, along with alkaloids, terpenoids, saponins, and other plant-derived compounds, have a variety of biological activities, such as regulating the lipid and glucose metabolism as well as having anti-inflammatory and cardioprotective effects. The benefits of whole-food strategies and dietary patterns that incorporate these compounds, including the Mediterranean and DASH diets, outweigh the use of these chemicals alone. Despite their benefits, standardizing dosages, improving bioavailability, and preserving quality control across sources is difficult. In addition to creating specialized phytomedicine and dietary plans, researchers need to carry out comprehensive multi-center clinical studies to completely understand their therapeutic potential. Nutraceuticals and functional foods containing phytopharmaceuticals are examples of evidence-based therapeutic practices that would enhance treatment outcomes and offer a comprehensive, safe, and accessible method for treating metabolic diseases.

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