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Advances in Research on Lipid-Lowering Mechanisms of Eight Medicinal Plants

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Abstract. Hyperlipidemia is a disease of fat metabolism or abnormal operation in healthcare, characterized by one or more of high total cholesterol (TC), high triglycerides (TG), high low-density lipoprotein cholesterol (LDL-C) and low high-density lipoprotein cholesterol (HDL-C) in blood. Hyperlipidemia is prone to cardiovascular and cerebrovascular diseases, obesity, diabetes, hyperinsulinemia and other diseases, posing a serious threat to human health. However, the commonly used chemical synthetic lipid-lowering drugs have obvious clinical effects, but the effect is biased to single and adverse reactions, such as adverse reactions of the nervous system, gastrointestinal reactions and liver damage. In recent years, a large number of literatures had reported that various medicinal plants or their active ingredients had lipid-lowering effects. Thus, finding safe and effective lipid-lowering components from natural medicines has a broad development prospects in research. In this review, I tried to explore the information of several active components of lipid-lowering plants and their lipid-lowering mechanisms, which may help future researchers develop new natural lipid-lowering drugs to treat hyperlipidemia.

Key words: Hyperlipidemia, Herbs, Lipid-Lowering Active Ingredients, Lipid-Lowering Mechanisms.

INTRODUCTION:

Herbal medicine, variously defined as herbs, plant medicines or botanical medicines, is a common treatment throughout the world. [1] Herbal products were not only limited to dietary uses, such as food and nutrition, but also as a unique role in the treatment of several diseases. Different parts of the plant, including flowers, fruits, seeds, leaves, berries, bark and roots could be used as an herbal medicine. [2] It was estimated that 80% rely on herbs to meet their primary health care needs. [1] It is well known that herbal medicine has been an important ingredient for thousands of years, the scientific studies and a lot of literatures which in the area is increasing more and more rapidly. It has been reported that some 75% of herbal medicines were developed through research on traditional medicinal plants, and 25% of prescription drugs belonged to higher plants. [3, 4] Many of the ingredients or preparations of the drug were extracted from medicinal plants, still used today for treating various diseases. Those medicinal plants made a great contribution to today's commercial pharmaceutical preparations. [5] This review explored the effects of medicinal plants such as blueberry, celery, dandelion, ginger, and green tea on serum TC, TG, LDL-C, and HDL-C by searching a large number of literatures. The purpose was to evaluate herbal candidates with lipid-lowering and weight-reducing effects, then providing a theoretical basis for the clinical application of natural medicinal plants and the development of new green healthy weight loss health products.

REGULATES THE EXPRESSION OF BLOOD LIPID-RELATED GENES AND IMPROVES LIPID METABOLISM

Studies had found that functional defects in human blood lipid-related genes and varying degrees of damage were one of the main causes of lipid metabolism disorders. Under a high-fat and high-cholesterol diet, it was easy to reduce

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the expression of blood lipid-related genes. The reduced expression of blood lipid-related genes resulted in decreased blood lipids and excretion, increased intracellular cholesterol, and increased blood cholesterol and triglyceride levels. Therefore, increased the activity of blood lipid-related gene expression, regulated HDL metabolism, and increased the rate of reverse cholesterol transport could accelerate the discharge of excess lipids and slow the deposition of excess lipids in the body.

Grape Seed

Studies have shown that grape seed contained two-thirds of the extractable flavonoids of grapes, containing the most common flavonoids, flavan-3-ol which was belonged to flavanols. Flavanols included catechins, epicatechins, 3-O-gallates and catechin dimers, oligomers and polymers. [6] Extracts could be mediated by regulation of genes involved in cholesterol, bile acid and lipid metabolism in liver and adipose tissues, thereby reducing hepatic lipid content, low-density lipoprotein (LDL), very low-density lipoprotein (VLDL) and plasma concentrations of total cholesterol. [7] The specific impact could be explained in the following three aspects:

Effect on liver gene expression: Microarray hybridization analysis of transcript profiles showed that the mRNA level of CYP7A1, a key enzyme controlled bile acid synthesis, was increased 2.4-fold in grape seed procyanidin extract (GSPE)-treated rats. It was indicated that GSPE could inhibit the increase of cholesterol by promoting bile acid production.

Effect on SHP expression: Small heterodimeric chaperone (SHP) is a nuclear receptor that emerges as a key co-transcription factor in the regulation of liposome homeostasis. Mutations in SHP were associated with mild obesity and insulin resistance. GSPE could exert hypolipidemic effect by inducing SHP expression.

Effect on apolipoprotein gene expression: study had shown that mRNA levels of lipoprotein lipases apolipoprotein C-I (ApoC-I), apolipoprotein C-II (ApoC-II) and apolipoprotein C-III (ApoC-III) were reduced in the GSPE-treated group. These changes led to functional changes in apolipoproteins that altered the distribution and utilization of TG and cholesterol in plasma, thereby inhibiting the accumulation of lipids in the liver. [8]

Indian Blackberry

Other studies [9] had shown that quercetin in Indian blackberry prevented the differentiation of mouse stromal cells into adipocytes by down-regulating the adipogenic gene.

REDUCE THE SYNTHESIS OF ENDOGENOUS LIPIDS SUCH AS TRIGLYCERIDE (TG) AND CHOLESTEROL (TC)

The human body could synthesize TC as needed or by synthesizing fatty acids due to overnutrition. Fatty acids were synthesized in the cytoplasm of liver, kidney, brain, lung, breast, adipose tissue, etc. The fatty acid synthesis of liver was the most active, and the synthesis ability was 8 to 9 times larger than that of adipose tissue. TG was most synthesized in the liver. Acetyl-CoA and Nicotinamide adenine dinucleotide phosphate (NADPH) were the synthetic raw materials for TG and TC. Acetyl-CoA was mainly derived from the aerobic oxidation of sugar, and NADPH was derived from the catalytic reaction of pentose phosphate pathway and cytoplasmic isocitrate dehydrogenase. The pathway involved various enzymes such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), catalase (CAT), superoxide dismutase (SOD), glutathione (GSH) transferase and reductase, etc. They could reduce the synthesis and release of endogenous lipids such as triglyceride (TG) cholesterol (TC) by affecting the activity of the above enzymes.

Celery

Celery (Apium graveolens L) was a medicine plant from the apiaceae family, which was one of the annual or perennial medicine plants grew in tropical and subtropical regions of Europe and Africa and Asia. [10] Celery's whole plant, seeds and essential oils are often used as food or medicine. It also had a long history of use in Ayurvedic and Unani medicines. Among the phytochemicals of celery, most were carbohydrates, phenols such as flavonoids, alkaloids and steroids. Phenolic acids and flavonoids were one of the reasons that celery was the most widely used medicinal plant in traditional medicine. [11] The main phenolic acids include caffeic acid, p-coumaric acid and ferulic

acid, and the main flavonoids include apigenin, luteolin and kaempferol. [12] Studies by Al Sa'aidi et al. had shown that celery seed (Apium graveolens) n-butanol extract could reduce the synthesis of endogenous lipids such as triglyceride (TG) cholesterol (TC) by improving lipid peroxidation and its anti-oxidation. Another study [13] also showed that diabetic rats which treatment with celery n-butanol water extract could increase alanine aminotransferase (ALT), superoxide dismutase (SOD), catalase (CAT), glutathione (GSH) activity. It was concluded that celery seed modified the insulin level and increased the activity of all antioxidant enzymes by affecting the production of pyruvate, acetyl-CoA, NADPH, etc.

Fenugreek

Fatty acid synthase (FAS) was responsible for the synthesis of acetyl-CoA, malonyl-CoA and NADPH. Many studies proved that NADPH-producing enzymes which in pentose phosphate pathway, were also critical for the biosynthesis of fatty acids and cholesterol. Treatment with Fenugreek water extract (AqE-TFG), [14] it could affect the activity of epididymal WAT lipogenic enzymes and reduce the availability of NADPH required for the biosynthesis of fatty acid and cholesterol, then leading to rapid decline in fat stores of high-fat diet (HFD)-fed rats.

INHIBITION OF ABSORPTION OF EXOGENOUS LIPIDS

Lipid absorption process: Generally, the lipids in food were mostly composed of long-chain fatty acids. Lipid transporters on the surface of the intestines were required to promote their transfer to intestinal cells when transporting. It was helped re-synthesizing triglycerides in the intestinal mucosa cells. Under the action of lipid transporters on the surface of the intestines, the lipid was absorbed in the form of chylomicrons into the blood circulation from the thoracic duct in the lymphatic system.

Green Tea

Tea (Camellia sinensis) had showed to inhibit the absorption of exogenous lipids.Laboratory studies showed that green tea played an important role in fat metabolism by reducing food intake, interrupting lipid emulsification and absorption. Another results of those studies showed that green tea could also increase energy expenditure through heat production, fat oxidation and fecal lipid excretion. [15] Green tea contained a characteristic polyphenolic compound called catechin. The main catechins presented were: epigallocatechin gallate (EGCG), epicatechin Augallate (ECG), epigallocatechin (EGC) and epicatechin (EC), and EGCG was the main form of tea catechin. [16, 17] The potent inhibitory effect of EGCG on pancreatic phospholipase A2 (PLA2) activity might be the main cause of reduced lipid absorption. [18] EGCG could form a complex with the surface PC of the lipid emulsion. The complex hindered the entry of PLA2 into the substrate. EGCG could also directly bind to the enzyme protein, altering enzyme's conformation and catalytic activity, then interfering with cellular uptake of lipids. [19] Grove K A, Sae−Tan S, Kennett M J, et al. had showed that [20] treatment with EGCG for 6 weeks, compared to high fat-fed control, EGCG dose-dependently inhibited phospholipid in a noncompetitive manner with respect to substrate concentration in vitro. Koo S I and Noh S K. [17] showed that EGCG could inhibit pancreatic lipase activity. [21] The hydroxyl moiety of EGCG interacted with the hydrophilic head of the PC. This interaction could increase the size of the emulsion droplets and thereby inhibits pancreatic lipase activity. [19] Another study showed that green tea extract also greatly inhibited the absorption of alpha-tocopherol and reduced the lymphatic output of alpha-tocopherol to 46%. [22]

INCREASE THE ACTIVITY OR AMOUNT OF ENZYMES THAT AFFECT LIPID METABOLISM

Studies had found that lecithin cholesterol acyltransferase (LCAT), hepatic lipase and lipoprotein lipase (LPL) were key enzymes in lipoprotein metabolism. Those key enzymes not only hydrolysed triglycerides in chylomicrons and very low density lipoproteins, but also promoted the conversion of catabolic products of CM and VLDL into high-density lipoproteins, ultimately regulated lipid metabolism. Changes in the biological activity of lipid metabolism enzymes could cause changes in lipid metabolism, leading to disorder of lipid metabolism. Therefore, by increasing the activity or quantity of enzymes that affected lipid metabolism, it could achieve the purpose of promoting lipid

metabolism. Fenugreek and ginger had a certain effect on improving lipid metabolism by affecting fat synthase, lipolytic enzymes and antioxidant enzymes and so on, the details as follows. [23]

Fenugreek

Fenugreek (Trigonella foenum-graecum) was an annual plant in the family Fabaceae, with leaves consisting of three small obovate to oblong leaflets. It was cultivated worldwide as a semiarid crop. It was also an old medicinal plant, which from India and Northern Africa. Fenugreek's seeds and its leaves extracts or powders for medicinal use had a long history in traditional medicine. [24] Trigonella foenum-graecum (TFG) seeds had been shown to have anti-hypoglycemic, lipid-lowing and anti-oxidant effects, could be used to induce labour, and reduce blood sugar levels, lose weight, anti-cholesterol, etc. [25]

Inhibition of fatty acid synthase: acetyl-CoA and NADPH as fatty acid synthase (FAS) to synthesize long-chain fatty acids. NADPH was produced by the pentose phosphate pathway, in which glucose-6-phosphate dehydrogenase (G6PD) and 6-phosphogluconate dehydrogenase (6PGD) were essential for the biosynthesis of NADPH. [26] Parveen Kumar et al. [27] treated an aqueous extract of Trigonella foenum-graecum seeds (AqE-TFG) to regulate activity of lipogenic enzymes FAS and G6PD in liver and epididymis brown adipose tissue (WAT). The results showed reduced availability of NADPH for fatty acid and cholesterol biosynthesis, leading to a rapid decline in fat storage of HFD-fed rats.

Increased activity of antioxidant enzymes: growth hormone deficiency (GHD), superoxide dismutase (SOD) and catalase (CAT) activities were decreased in rats with dyslipidemia induced by HFD. Lipid peroxide levels were significantly decreased after administration of AqE-TFG for 21 days. The antioxidant enzymes GSH, SOD and CAT levels significantly rose. [27]

Inhibition of lipolytic enzyme activity: The decrease in lipase activity after several weeks of treatment with AqE-TFG showed that AqE-TFG inhibited the absorption of dietary fat in the intestine, and decreased the accumulation of triglycerides in various tissues of liver and WAT. [27, 28] Another study reported that fenugreek galactomannan, could form a viscous gel in the intestine, inhibiting the absorption of glucose and lipids, ultimately improved dyslipidemia in HFD obese rats. [28]

Ginger

Ginger was the underground rhizome of the Zingier officinal plant belonging to the Zingibeaceae family. It had been widely used in traditional Chinese medicine, Ayurveda and Unani-Tibb since ancient times. Ginger could be used to treat various diseases including arthritis, rheumatism, dyspepsia, vomiting, hypertension, obesity and cardiovascular disease. [32] Ginger had been proven to have various pharmacological activities over the centuries, especially anti-inflammatory and anti-lipid activities. [29] Ahmida and Abuzogaya [30] suggested that consumption of ginger could aid in the treatment of obesity and other diseases related to cardiovascular disease in rats. Alizadeh et al. [29] showed ginger had a significant lipid lowering effects in patients with hyperlipidemia. Furthermore, ginger produced a significant hypoglycemic effect in diabetic rats. [31] Ginger's mechanism of improving blood lipid characteristics could be divided into the following points:

Ethanolic extract of Zingiber officinale Roscoe could protect tissues from lipid peroxidation. The extract also showed significant lipid-lowering activity in diabetic rats. Increases bile acid biosynthesis activity: Ginger increased the activity of hepatic cholesterol-7-hydroxylase, the rate-limiting enzyme in bile acids biosynthesis, thereby stimulating the conversion of cholesterol to bile acids. Then, ginger increased excretion of bile acids to reduce cholesterol biosynthesis in the liver. These processes finally led to the elimination of cholesterol in the body. Inhibition of hydrolase activity of triolein: Triolein was an unsaturated glyceride which is hydrolyzed to glycerol and oleic acid by its hydrolase. Ginger could effectively inhibit the hydrolysis of triolein, thereby reducing the level of triacylglycerol in plasma. [33] Effect on enzymes during oxidation: Reported by Ansari MN, et al. [34] Ethanolic Z. officinale extract pretreatment for 20 days in isoproterenol-treated rats significantly increased the levels of endogenous myocardial antioxidants and decreased the levels of serum marker enzymes. It had also been reported [35] that diet ginger could regulate OFR scavenging enzyme, reduced glutathione(GSH), GSH-dependent enzyme glutathione peroxidase (GPX), valley Glutathione reductase (GR) and glutathione-S-transferase (GST) to improve lipid peroxidation.

Ginger had been reported to interfere with the activity of certain digestive enzymes. In animals with diabetes, apolipoprotein E gene deficiency, and high lipid diets, ginger significantly reduced serum total cholesterol, LDL, VLDL, and triglycerides, and elevated HDL. [32, 36, 37, 38]

ANTI-LIPID PEROXIDATION, SCAVENGING FREE RADICALS

Peroxidation refers to an imbalance between oxidation and antioxidant activity in the body, which tended to oxidize, resulting in the production of a large amount of oxidized intermediate. It was also known as oxidative stress, which was the result of excessive production of free radicals or reduction of antioxidant levels. Increased oxidative stress was associated with metabolic syndrome, such as disorders of fat metabolism, abnormal regulation of the redox state of adipose tissue, leading to dyslipidemia, hyperlipidemia and obesity. [39] More and more evidence showed that the phytochemicals of natural plant extracts exerted potential antihyperlipidemic effects through different mechanisms. [40] The active ingredients and lipid-lowering mechanisms of artichoke, dandelion, and Indian blackberry will be elaborated below.

Cynara Scolymus

Cynara scolymus was an ancient herbaceous perennial plant and a medicinal edible plant from the southern Mediterranean region of North Africa. Its leaves had been used in herbal medicine widely. Since ancient times, it had the ability to promote bile excretion, liver protection, diuresis, antioxidant activity, anti-inflammatory, and inhibition of cholesterol biosynthesis. [39, 40] The polyphenol content in leaves could be used in dyslipidemia and diabetes as secondary metabolites. These benefits were mainly attributed to the ability of phenolic compounds, including flavonoids, phenolic acids, lignans and stilbene. [41] The ethanol extract of Cynara scolymus leaves could reduce blood lipids, due to its resistance oxidative activity. [42] The above contents provided the evidence that Cynara scolymus could play an important role in treat hyperlipidemia. It well knows that the body had an effective defense mechanism to prevent and neutralize damage caused by free radicals. This defense mechanism consisted of a group of antioxidant enzymes such as SOD, CAT and GSH. These enzymes formed a mutually supportive anti-ROS defense team. [43, 44] A study from Salem MB et al. [42] showed that administration of ethanol extract from Cynara scolymus leaves increased the levels of these enzymes in pancreatic tissues. In addition, Ben Salem et al. [45] it was revealed that chlorogenic acid in cynarin was considered to be the cause of its antihyperlipemia. This study had showed that long-term use of acidic chlorogenic acid improved lipid profiles and skeletal muscle glucose uptake, which also improved fasting blood glucose levels, glucose tolerance insulin sensitivity and dyslipidemia.

Taraxacum Officinale

Dandelion (Taraxacum officinale) Weber was a member of the Asteraceae family, native to Europe, widely distributed in the tropics, cool elevation of 1,200-1,500 meters above sea level and warmer temperate regions of the northern hemisphere. [46] In traditional Chinese medicine, it was known as a non-toxic herbal medicine with special choleretic, diuretic, anti-rheumatic and anti-inflammatory properties. In fact, dandelion contained a variety of phytochemicals, including caffeic acid, chlorogenic acid, luteolin and luteolin 7-glucoside. The biological activity of dandelion was actively explored in various fields of human health. In a study, [47] mice fed a high fat and cholesterol diet were evaluated using leaf-like mixed plant extracts which including dandelion. During the experiment, a significant improvement in lipid peroxidation was observed in various organs. Flowers from dandelion had potential antioxidant effect. Their leaf extract was also an effective hydrogen donor, hydrogen peroxide scavenger and reducing agent. [53, 54, 55]

Recently, chlorogenic acid (CGA) had been found in the roots of dandelion and had been identified as an effective antioxidant. CGA was involved in glucose and lipid metabolism. It could inhibit oxidative stress markers such as malondialdehyde and glutathione, increase ROS scavenging enzyme production, then inhibiting oxidative stress in the liver. [48]

Glucose might produce ROS in beta cells, and the process of ROS formation involved auto-oxidation, oxidative phosphorylation, glycosylation, and glucosamine pathways. [50] Excessive ROS production was prone to oxidative stress, which in turn produced glucose toxicity. [49] Dandelion extract could reduce liver lipid accumulation by activating phosphorylation of AMP and AMPK [51] to inhibit the toxic effect of elevated free fatty acid concentration on beta cells. [52] It could also improve insulin secretion and impair gene expression, restore normal glucose levels, then inhibited glucose-induced oxidative stress and abnormal blood lipid metabolism.

Syzygium Cumini

The genus Syzygium was one of the genera of the myrtle family Myrtaceae which was native to the tropics, particularly to tropical America and Australia. It had a worldwide, although highly uneven, distribution in tropical and subtropical regions. The genus comprised about 1 100 species, its origin extended from Africa and Madagascar to eastern South Asia. [56]

The leaves, stem bark, flowers, roots, fruits, essential oils of Syzygium cumini had anti-hyperglycemia, anti-inflammatory, anti-bacterial, cardioprotective and anti-oxidant effects, and could be used to treat various diseases such as astringents, ascorbic acid, diuretics, anti-diabetes and chronic diarrhea. [57, 58] The main anti-oxidation effect will be introduced below:

The main antioxidant components were bioactive polyphenols including anthocyanidins, ellagic acid, ellagitannins, etc. The seed extract of Syzygium cumini also contained other chemicals such as triterpenoids, oleic acid, essential oils, glycosides, saponins and several flavonoids. [58, 59]

The main antioxidant mechanism of Syzygium cumini: There was a close relationship between insulin receptor (IR) and dyslipidemia. In fact, insulin receptor (IR) increased 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase activity, which was an enzyme responsible for cholesterol synthesis and decreased lipoprotein lipase (LPL) activity by mobilizing free fatty acid (FFA) from obese warehouses. [59] Syzygium cumini could inhibit the activity of HMG-CoA to against hyperlipidemia. [60] According to the results of Havsteen B. H. [61], the flavonoids found in Syzygium cumini could explain this activity. Flavonoids increased the expression of cAMP-dependent phosphokinase, an enzyme responsible for inhibiting HMG-CoA reductase, it made HFD- Plasma lipoprotein and fatty acid composition returned to normal levels in streptozotocin -induced diabetic rats.

REDUCE INSULIN RESISTANCE AND PROMOTE LIPID METABOLISM

Leptin was a hormone-like protein secreted mainly by adipose tissue. It played an important role in regulating body feeding, energy metabolism and suppressing appetite. As the fat increased, the tissue weight and serum leptin levels also tend to increase. When body was in a high level of leptin secretion for a long time, the brain leptin receptor received high-intensity stimulation for a long time, which led to reducing the sensitivity of leptin and producing leptin resistance. Leptin resistance made excessive intake due to appetite uncontrollably, then the increase of fat deposition in adipose tissue affected the ability of insulin to transport glucose, ultimately led to aggravating the degree of impaired insulin sensitivity, insulin resistance and dyslipidemia. [62] Therefore, the decrease in leptin level could be used as an indicator of reduced insulin resistance and improved lipid metabolism.

Adiponectin was an insulin-sensitizing hormone composed mainly of a large number of aggregated fat cells, and it was an endogenous biologically active polypeptide secreted by fat cells. Adiponectin stimulated fatty acid oxidation by activating AMPK in peripheral tissues. It promoted glucose uptake in skeletal muscle and inhibited glucose production in the liver to improve insulin resistance in mice. So, adiponectin could also be used as an indicator of insulin resistance in experiments.

Fenugreek

In the study of In Kumar P, Bhandari U, Jamadagni S [27], consumption of high caloric intake in form of HFD for a period of 28 days induced obesity in rats. After treatment with fenugreek water extract (AqE-TFG), the reduction of leptin levels indicated that AqE-TFG treatment caused significant adipocytes loss. This observation was further supported by the AqE-TFG mediated reductions in WAT weights and adiposity index of HFD-fed rats. Another result of this study was also stated that AqE-TFG mediates the reduction of homeostatic model assessment- insulin resistance in high-fat diets, and the increase in quantitative insulin sensitivity check *index*. This indicated that AqE-TFG had an improvement in insulin sensitivity and insulin resistance. In the study of in Kumar P, Bhandari U, Jamadagni S [27], the experimental data showed that the adiponectin in the high-fat diet mice treated with AqE-TFG was at a relatively high level, it indicated that AqE-TFG could protect against metabolic disorders and reduce insulin resistance to promote lipid metabolism.

INHIBITS PLATELET AGGREGATION, IMPROVES BLOOD RHEOLOGY ABNORMALITIES, AND REDUCES BLOOD VISCOSITY

Thromboxane was a metabolite of arachidonic acid. The two major thromboxanes were thromboxane A2 (TXA2) and thromboxane B2 (TXB2). Thromboxane is named for its role in clot formation and thrombosis. It could cause smooth muscle contraction and platelet aggregation. [63] Prostacyclin, which also called prostaglandin I2 or PGI2, was a prostaglandin member of the eicosanoid family of lipid molecules. It was an effective vasodilator, mainly prevented platelet embolism and inhibited platelet activation. Under abnormal conditions, the homeostatic mechanism such as cardiovascular and homeostasis between TXA2 and PGI2 in plasma or tissue was imbalanced, resulting in platelet aggregation, vasospasm contraction or thrombosis.

Ginger

In imbalanced state between TXA2 and PGI2, Prostacyclin has a half-life of 42 seconds and is rapidly metabolized to 6-keto-PGF1. Ginger had a significant dose-dependent inhibition of arachidonic acid-induced platelet aggregation, cyclooxygenase-derived thromboxane and prostaglandins and prostacyclin synthesis. The results of Cawello, W, et al. [64] and Thomson M, et al. [65] were consistent. Their studies had showed that TXB2 levels were significantly reduced in rats given ginger. Ginger water extract inhibited the biosynthesis of *6-keto* prostaglandin F1α (6-keto-F1α) in the aorta ring of rat labeled AA. [66] Srivastava, K. C. study [67] showed that the lipoxygenase product was also reduced at higher doses of Aqueous-ginger extract. Those indicated that ginger could reduce platelet aggregation, improve blood viscosity, blood rheology and various lipid components in hyperlipidemia patients.

CONCLUSION

At present, phytochemicals are widely used in various weight loss and lipid-lowering products due to their low toxicity, high safety and remarkable effects. However, the composition of phytochemicals is complex, and many components interact with each other. It is difficult to analyze them separately. With the application of cell biology and molecular biology techniques, the lipid-lowering pathways and action links of some lipid-lowering medicinal plants had been gradually elucidated and could be broadly classified into the following categories: reducing the absorption of exogenous lipids, reducing the synthesis and release of endogenous lipids, anti-oxidation, increasing the activity and quantity of high-density lipoprotein cholesterol (HDL-C). Understanding the lipid-lowering mechanisms of various phytochemicals could be a great help in diseases such as hyperlipidemia, atherosclerosis, arrhythmia and vasodilation. This review summarized eight medicinal plants that were effective in lowering total cholesterol, serum triglycerides, LDL-C, and increasing serum HDL levels by reviewing published literature. Regulated the expression of blood lipid-related genes (grape seed, Indian blackberry), reduced the synthesis of endogenous lipids such as triglyceride (TG) cholesterol (TC) (celery, fenugreek), inhibition of absorption of exogenous lipids (green tea), increased the activity or amount of enzymes that affect lipid metabolism (ginger), anti-lipid peroxidation, scavenged free radicals (artichoke, dandelion), reduced insulin resistance (fenugreek), inhibited platelet aggregation (ginger).

In fact, a medicinal plant could affect the lipid metabolism pathway in many ways, and two or more medicinal plants could simultaneously have a mechanism of action. Up to now, the lipid-lowering mechanism of some medicinal plants was still not very clear. Therefore, understanding the lipid-lowering mechanism of various phytochemicals will help to develop new, natural, safe and high-efficiency lipid-lowering drugs.

REFERENCES

1. World Health Organization (WHO) [Accessed: April 19, 2013] ; Fact Sheet No 134. 2008 Dec;http: //www. Who. int/ mediacentre/factsheets/fs134/en/
2. Pan S Y, Litscher G, Gao S H, et al. Historical perspective of traditional indigenous medical practices: the current renaissance and conservation of herbal resources [J]. Evidence-Based Complementary and Alternative Medicine, 2014, 2014.
3. Sahoo N, Manchikanti P, Dey S. Herbal drugs: standards and regulation [J]. Fitoterapia, 2010, 81(6): 462-471.
4. Wang M Y, West B J, and Jensen C J, et al. Morinda citrifolia (Noni): a literature review and recent advances in Noni research [J]. Acta Pharmacologica Sinica, 2002, 23(12): 1127-1141.

5. Herbal medicine: biomolecular and clinical aspects [M]. CRC Press, 2011.
6. Seo K H, Bartley G E, Tam C, et al. Chardonnay grape seed flour ameliorates hepatic steatosis and insulin resistance via altered hepatic gene expression for oxidative stress, inflammation, and lipid and ceramide synthesis in diet-induced obese mice[J]. PloS one, 2016, 11(12): e0167680.
7. Kim H, Bartley G E, Arvik T, et al. Dietary supplementation of chardonnay grape seed flour reduces plasma cholesterol concentration, hepatic steatosis, and abdominal fat content in high-fat diet-induced obese hamsters[J]. Journal of agricultural and food chemistry, 2014, 62(8), 1919-1925.
8. Del Bas J M, Fernández-Larrea J, Blay M, et al. Grape seed procyanidins improve atherosclerotic risk index and induce liver CYP7A1 and SHP expression in healthy rats[J]. The FASEB journal, 2005, 19(3): 479-481.
9. Seo Y S, Kang O H, Kim S B, et al. Quercetin prevents adipogenesis by regulation of transcriptional factors and lipases in OP9 cells [J]. International journal of molecular medicine, 2015, 35(6): 1779-1785.
10. Rubatzky V E, Yamaguchi M. World vegetables: principles, production, and nutritive values [M]. Springer Science & Business Media, 2012.
11. Bhattacharjee S K. Handbook of medicinal plants [M]. Aavishkar Publishers, 2000.
12. Yao Y, Sang W, Zhou M, et al. Phenolic composition and antioxidant activities of 11 celery cultivars[J]. Journal of Food Science, 2010, 75(1): C9-C13.
13. Al-Sa'aidi J A A, Alrodhan M N A, Ismael A K. Antioxidant activity of n-butanol extract of celery (Apium graveolens) seed in streptozotocin-induced diabetic male rats [J]. Research in Pharmaceutical Biotechnology, 2012, 4(2): 24-29.
14. De Melo C L, Queiroz M G R, Arruda Filho A C V, et al. Betulinic acid, a natural pentacyclic triterpenoid, prevents abdominal fat accumulation in mice fed a high-fat diet [J]. Journal of agricultural and food chemistry, 2009, 57(19): 8776-8781.
15. Huang J, Wang Y, Xie Z, et al. The anti-obesity effects of green tea in human intervention and basic molecular studies[J]. European journal of clinical nutrition, 2014, 68(10): 1075.
16. Yang C S, Zhang J, Zhang L, et al. Mechanisms of body weight reduction and metabolic syndrome alleviation by tea [J]. Molecular nutrition & food research, 2016, 60(1): 160-174.
17. Koo S I, Noh S K. Green tea as inhibitor of the intestinal absorption of lipids: potential mechanism for its lipid-lowering effect [J]. The Journal of nutritional biochemistry, 2007, 18(3): 179-183.
18. Borgström B. Importance of phospholipids, pancreatic phospholipase A2, and fatty acid for the digestion of dietary fat: in vitro experiments with the porcine enzymes [J]. Gastroenterology, 1980, 78(5): 954-962.
19. Shishikura Y, Khokhar S, Murray B S. Effects of tea polyphenols on emulsification of olive oil in a small intestine model system [J]. Journal of agricultural and food chemistry, 2006, 54(5): 1906-1913.
20. Grove K A, Sae‐Tan S, Kennett M J, et al. (-) - Epigallocatechin‐3‐gallate Inhibits Pancreatic Lipase and Reduces Body Weight Gain in High Fat‐Fed Obese Mice [J]. Obesity, 2012, 20(11): 2311-2313.
21. Armand M, Pasquier B, André M, et al. Digestion and absorption of 2 fat emulsions with different droplet sizes in the human digestive tract–[J]. The American journal of clinical nutrition, 1999, 70(6): 1096-1106.
22. Wang S, Noh S K, Koo S I. Green tea catechins inhibit pancreatic phospholipase A2 and intestinal absorption of lipids in ovariectomized rats [J]. The Journal of nutritional biochemistry, 2006, 17(7): 492-498.
23. Feingold K R, Grunfeld C. Introduction to lipids and lipoproteins [M]//Endotext [Internet]. MDText. Com, Inc., 2018.
24. Smith M. Therapeutic applications of fenugreek [J]. Alternative Medicine Review, 2003, 8(1): 20-27.
25. Vinayagam R, Xu B. Antidiabetic properties of dietary flavonoids: a cellular mechanism review [J]. Nutrition & metabolism, 2015, 12(1): 60.
26. Wakil S J, Abu-Elheiga L A. Fatty acid metabolism: target for metabolic syndrome [J]. Journal of lipid research, 2009, 50(Supplement): S138-S143.
27. Kumar P, Bhandari U, Jamadagni S. Fenugreek seed extract inhibit fat accumulation and ameliorates dyslipidemia in high fat diet-induced obese rats [J]. BioMed research international, 2014, 2014.
28. Hamden K, Jaouadi B, Carreau S, et al. Inhibitory effect of fenugreek galactomannan on digestive enzymes related to diabetes, hyperlipidemia, and liver-kidney dysfunctions [J]. Biotechnology and Bioprocess Engineering, 2010, 15(3): 407-413.
29. Alizadeh-Navaei R, Roozbeh F, Saravi M, et al. Investigation of the effect of ginger on the lipid levels. A double blind controlled clinical trial[J]. Saudi Med J, 2008, 29(9): 1280-4.

30. Ahmida M H, Abuzogaya M H. The effects of oral administration of green tea and ginger extracts on serum and hepatic lipid content in rats fed a hyperlipidemic diet[J]. Journal of Applied Sciences Research, 2009 (October): 1709-1713.
31. Elshater A E, Salman M M A, Moussa M M A. Effect of ginger extract consumption on levels of blood glucose, lipid profile and kidney functions in alloxan induced-diabetic rats [J]. Egyptian Academic Journal of Biological Sciences, 2009, 2(1): 153-162.
32. Rong X, Peng G, Suzuki T, et al. A 35-day gavage safety assessment of ginger in rats [J]. Regulatory Toxicology and Pharmacology, 2009, 54(2): 118-123.
33. Bhandari U, Pillai K K. Effect of ethanolic extract of Zingiber officinale on dyslipidaemia in diabetic rats [J]. Journal of ethnopharmacology, 2005, 97(2): 227-230.
34. Ansari M N, Bhandari U, Pillai K K. Ethanolic Zingiber officinale R. extract pretreatment alleviates isoproterenol-induced oxidative myocardial necrosis in rats [J]. 2006.
35. Ahmed R S, Suke S G, Seth V, et al. Protective effects of dietary ginger (Zingiber officinales Rosc.) on lindane‐induced oxidative stress in rats[J]. Phytotherapy Research, 2008, 22(7): 902-906.
36. Thomson M, Al-Qattan K K, Al-Sawan S M, et al. The use of ginger (Zingiber officinale Rosc.) as a potential anti-inflammatory and antithrombotic agent[J]. Prostaglandins, leukotrienes and essential fatty acids, 2002, 67(6): 475-478.
37. Fuhrman B, Rosenblat M, Hayek T, et al. Ginger extract consumption reduces plasma cholesterol, inhibits LDL oxidation and attenuates development of atherosclerosis in atherosclerotic, apolipoprotein E-deficient mice[J]. The Journal of nutrition, 2000, 130(5): 1124-1131.
38. Verma S K, Singh M, Jain P, et al. Protective effect of ginger, Zingiber officinale Rosc on experimental atherosclerosis in rabbits [J]. 2004.
39. Gebhardt R. Antioxidative and protective properties of extracts from leaves of the artichoke (Cynara scolymus L.) against hydroperoxide-induced oxidative stress in cultured rat hepatocytes [J]. Toxicology and applied pharmacology, 1997, 144(2): 279-286.
40. Kraft K. Artichoke leaf extract—recent findings reflecting effects on lipid metabolism, liver and gastrointestinal tracts [J]. Phytomedicine, 1997, 4(4): 369-378.
41. Manach C, Scalbert A, Morand C, et al. Polyphenols: food sources and bioavailability [J]. The American journal of clinical nutrition, 2004, 79(5): 727-747.
42. Salem M B, Kolsi R B A, Dhouibi R, et al. Protective effects of Cynara scolymus leaves extract on metabolic disorders and oxidative stress in alloxan-diabetic rats[J]. BMC complementary and alternative medicine, 2017, 17(1): 328.
43. Amresh G, Zeashan H, Gupta R J, et al. Gastroprotective effects of ethanolic extract from Cissampelos pareira in experimental animals [J]. Journal of natural medicines, 2007, 61(3): 323-328.
44. Amresh G, Rao C V, Singh P N. Antioxidant activity of Cissampelos pareira on benzo (a) pyrene-induced mucosal injury in mice[J]. Nutrition Research, 2007, 27(10): 625-632.
45. Salem M B, Affes H, Ksouda K, et al. Pharmacological studies of artichoke leaf extract and their health benefits [J]. Plant foods for human nutrition, 2015, 70(4): 441-453.
46. Honek A, Martinkova Z, Saska P, et al. Role of post-dispersal seed and seedling predation in establishment of dandelion (Taraxacum agg.) plants[J]. Agriculture, ecosystems & environment, 2009, 134(1-2): 126-135.
47. Kim M Y, Cheong S H, Kim M H, et al. Leafy vegetable mix supplementation improves lipid profiles and antioxidant status in C57BL/6J mice fed a high fat and high cholesterol diet [J]. Journal of medicinal food, 2009, 12(4): 877-884.
48. Del Rio D, Stewart A J, Pellegrini N. A review of recent studies on malondialdehyde as toxic molecule and biological marker of oxidative stress[J]. Nutrition, metabolism and cardiovascular diseases, 2005, 15(4): 316-328.
49. Robertson R P, Zhou H, Zhang T, et al. Chronic oxidative stress as a mechanism for glucose toxicity of the beta cell in type 2 diabetes [J]. Cell biochemistry and biophysics, 2007, 48(2-3): 139-146.
50. Robertson R P, Harmon J, Tran P O T, et al. β-cell glucose toxicity, lipotoxicity, and chronic oxidative stress in type 2 diabetes [J]. Diabetes, 2004, 53(suppl 1): S119-S124.
51. Davaatseren M, Hur H J, Yang H J, et al. Taraxacum official (dandelion) leaf extract alleviates high-fat diet-induced nonalcoholic fatty liver[J]. Food and chemical toxicology, 2013, 58: 30-36.
52. Boden G, Shulman G I. Free fatty acids in obesity and type 2 diabetes: defining their role in the development of insulin resistance and β‐cell dysfunction [J]. European journal of clinical investigation, 2002, 32: 14-23.

53. González-Castejón M, Visioli F, Rodriguez-Casado A. Diverse biological activities of dandelion [J]. Nutrition reviews, 2012, 70(9): 534-547.
54. Czinner E, Hagymasi K, Blazovics A, et al. The in vitro effect of Helichrysi flos on microsomal lipid peroxidation[J]. Journal of ethnopharmacology, 2001, 77(1): 31-35.
55. Wirngo F E, Lambert M N, Jeppesen P B. The physiological effects of dandelion (Taraxacum officinale) in type 2 diabetes[J]. The review of diabetic studies: RDS, 2016, 13(2-3): 113.
56. Ayyanar M, Subash-Babu P. Syzygium cumini (L.) Skeels: A review of its phytochemical constituents and traditional uses[J]. Asian Pacific journal of tropical biomedicine, 2012, 2(3): 240-246.
57. Aqil F, Gupta A, Munagala R, et al. Antioxidant and antiproliferative activities of anthocyanin/ellagitannin-enriched extracts from Syzygium cumini L.(Jamun, the Indian Blackberry)[J]. Nutrition and cancer, 2012, 64(3): 428-438.
58. Li L, Adams L S, Chen S, et al. Eugenia jambolana Lam. berry extract inhibits growth and induces apoptosis of human breast cancer but not non-tumorigenic breast cells [J]. Journal of agricultural and food chemistry, 2009, 57(3): 826-831.
59. Sharma A K, Bharti S, Kumar R, et al. Syzygium cumini ameliorates insulin resistance and β-cell dysfunction via modulation of PPARγ, dyslipidemia, oxidative stress, and TNF-α in type 2 diabetic rats[J]. Journal of pharmacological sciences, 2012, 119(3): 205-213.
60. Ravi K, Rajasekaran S, Subramanian S. Antihyperlipidemic effect of Eugenia jambolana seed kernel on streptozotocin-induced diabetes in rats [J]. Food and Chemical Toxicology, 2005, 43(9): 1433-1439.
61. Havsteen B H. The biochemistry and medical significance of the flavonoids[J]. Pharmacology & therapeutics, 2002, 96(2-3): 67-202.
62. Reaven G M. Pathophysiology of insulin resistance in human disease [J]. Physiological reviews, 1995, 75(3): 473-486.
63. Abe T, Takeuchi K, Takahashi N, et al. Rat kidney thromboxane receptor: molecular cloning, signal transduction, and intrarenal expression localization[J]. The Journal of clinical investigation, 1995, 96(2): 657-664.
64. Cawello W, Schweer H, Müller R, et al. Metabolism and pharmacokinetics of prostaglandin E 1 administered by intravenous infusion in human subjects[J]. European journal of clinical pharmacology, 1994, 46(3): 275-277.
65. Thomson M, Al-Qattan K K, Al-Sawan S M, et al. The use of ginger (Zingiber officinale Rosc.) as a potential anti-inflammatory and antithrombotic agent[J]. Prostaglandins, leukotrienes and essential fatty acids, 2002, 67(6): 475-478.
66. Srivastava K C. Aqueous extracts of onion, garlic and ginger inhibit platelet aggregation and alter arachidonic acid metabolism [J]. Biomedica biochimica acta, 1984, 43(8-9): S335-46.
67. Srivastava K C. Isolation and effects of some ginger components on platelet aggregation and eicosanoid biosynthesis [J]. Prostaglandins, Leukotrienes and Medicine, 1986, 25(2-3): 187-198.