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Review Article

Significance of traditional herbal medicine for dyslipidemia

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Abstract: Dyslipidemia is a multifactorial disorder that is a causative factor and risk factor for cardiovascular disease. The incidence of dyslipidemia is expected to increase because of the presence of comorbidities. Although several lipid-lowering drugs have been developed and approved, they are not completely effective and are associated with side effects. Traditional herbal medicine (THM) represents an alternative and complementary approach for managing dyslipidemia because of its low toxicity and beneficial effects, such as anti-inflammatory and antioxidant effects. This review focuses on our current understanding of the antidyslipidemic effect of THMs and discusses the associated regulatory mechanisms. The current findings indicate that THM may lead to the development of novel therapeutic regimens for dyslipidemia.

Keywords: Dyslipidemia, traditional herbal medicine, lipid-lowering drugs, Scutellariae Radix, Alismatis Rhizoma, Atractylodis Rhizoma Alba

Introduction

Dyslipidemia refers to the abnormal levels of lipid substances in plasma. It is characterized by elevated levels of serum triglycerides (TGs), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-c) and reduced levels of high-density lipoprotein cholesterol (HDL-c) [1]. Dyslipidemia includes hypertriglyceridemia, hypercholesterolemia, hyper-LDL cholesterolemia, and hypo-HDL cholesterolemia [2]. These conditions can result from poor diet, tobacco exposure, genetic factors, or cardiovascular disease with severe complications. The prevalence of dyslipidemia has increased worldwide with modern lifestyle changes and is markedly increased in older individuals and those with a high body mass index [3]. The World Health Organization estimated that the prevalence of hypercholesterolemia in adults increased from 9.0% to 20.7% between 2007 and 2018 [4]. Moreover, the prevalence of dyslipidemia has continued to increase in Korea-from one in four adults to two in five adults in 2022 [5].

A serious concern regarding dyslipidemia is its associated comorbidities. Dyslipidemia is a multifactorial disorder that is accompanied by metabolic syndromes, such as obesity, diabetes, fatty liver, hypertension, coronary artery disease, hyperinsulinemia, type 2 diabetes mellitus, and hyperglycemia [6]. According to epidemiological studies, the most common combination in middle-aged and older patients is hyperlipidemia coupled with hypertension [7]. Over 70% of individuals treated for hypertension received concurrent treatment for dyslipidemia (hyper-LDL-c ≥ 130 mg/dL, hyper-TG ≥ 200 mg/dL, or hypo-HDL-c < 40 mg/dL) [8]. Patients with diabetes have a higher risk of having dyslipidemia compared with those without diabetes. A substantial proportion (87%) of individuals with diabetes have dyslipidemia (hyper-LDL-c ≥ 100 mg/dL, hyper-TG ≥ 200 mg/dL, or hypo-HDL-c < 40 mg/dL), and the incidence is expected to increase with the rapidly growing older population. Dyslipidemias are associated with severe diseases of other organ systems, including acute pancreatitis [9], nonalcoholic fatty liver disease [10], allergic rhinitis [11], and

COVID-19 [12] as well as endocrine and metabolic disorders.

Traditional herbal medicine (THM) constitutes a major part of alternative and complementary medicine for the management of metabolic disorders [13, 14]. It has the potential to enhance therapeutic effects with fewer side effects. The role of herbal medicines in inflammation and oxidative stress is well known [15]. THM may also exhibit activity in many other diseases including dyslipidemia [16, 17]. In this review, we focus on our current understanding of the antidyslipidemic effect of THMs and discuss the associated regulatory mechanisms based on single herbal medicines and prescriptions frequently used to treat dyslipidemia.

Conventional therapy for dyslipidemia

The most commonly prescribed lipid-lowering drugs include statins, ezetimibe, cholestyramine, nicotinic acid, fibrates, omega-3, and their combinations [18]. Statins, which inhibit 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase, are considered the first-line therapy for reducing plasma cholesterol levels by inhibiting the mevalonate pathway and preventing cholesterol biosynthesis [19]. Blocking the activity of this enzyme decreases intrahepatic de novo level of cholesterol, upregulates the normal expression of LDL receptor (LDLR), and increases the hepatic clearance of LDL particles, resulting in reduced LDL-c levels in the bloodstream [20]. Ezetimibe is a selective inhibitor of cholesterol absorption that binds and blocks Niemann-Pick C1-like 1 (NPC1L1) protein, which is responsible for the absorption of biliary and dietary cholesterol from the small intestine, resulting in an incremental reduction in LDL-c levels [21]. Cholestyramine is used as an adjunct to reduce elevated serum cholesterol levels by sequestering intestinal bile acids. This results in the enhanced conversion of cholesterol to bile acids in the liver, which is normally regulated by the negative feedback of bile acids [22]. Nicotinic acid reduces circulating lipid levels including TGs, very-low-density lipoprotein (VLDL) cholesterol, and LDL-c, by reducing the synthesis of the LDL precursor and VLDL, while increasing HDL-c levels [23]. Fibrates are PPAR-α agonists that reduce plasma TG levels and increase HDL-c levels by initiating catabolism through β-oxidation, stimulating cellular fatty acid uptake, reducing TG levels, promoting lipoprotein lipase (LPL) activity, and reversing cholesterol transport [24]. Omega-3 (n-3) also substantially reduces blood TG levels by increasing fatty acid oxidation, which suppresses hepatic lipogenesis and acts as a poor substrate for TG-synthesizing enzymes [25].

Several approaches have been used to develop targeted agents for lipid-lowering therapies. Lomitapide inhibits microsomal TG transfer protein, which is responsible for the formation of lipoproteins, such as chylomicron (CM) precursors in the small intestine and VLDL precursors in the liver [26]. Mipomersen is an antisense oligonucleotide inhibitor that targets apolipoprotein B-100 (apoB-100) packaged into VLDLs in the liver [27]. RGX-501 is a novel gene therapy that corrects defective hepatic LDLR in patients with familial hypercholesterolemia (HoFH) [28, 29]. Sebelipase restores the levels of lysosomal acid lipase (LIPA), which hydrolyzes TG and cholesteryl ester in the lysosomes of the liver in patients with LIPA deficiency [30]. In plasma, Glybera (alipogene tiparvovec) restores the LPL activity required to hydrolyze TGs within CMs and VLDL in patients with LPL deficiency [31]. Evolocumab, alirocumab, and bococizumab are proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors and markedly lower LDL-c levels [32]. Volanesorsen is an antisense inhibitor of Apo C-III formation that can inhibit LPL and reduce TG levels [33]. Evinacumab is an anti-angiopoietin-like protein 3 (ANGPTL3) inhibitor that is effective at reducing LDL-c levels in patients with HoFH [34]. TThe antisense oligonucleotide Apo(a)-LRx inhibits LP(a) synthesis by disrupting apo(a) synthesis [35]. In peripheral cells, MEDI6012 is a recombinant human lecithin cholesterol acyltransferase (LCAT) that restores LCAT activity in patients with LCAT deficiency [36]. CSL112 is an infused apoA-I peptide that increases cholesterol efflux [37]. Continued drug development and new strategies for lipid reduction are currently underway. Combining medications is occasionally necessary for the effective treatment of lipid abnormalities in patients with mixed dyslipidemia with comorbidities [38]. Although statin monotherapy does not always achieve the desired LDL-c level, combination therapy with other lipid-reducing agents is underutilized. For example, ezetimibe may be used in combination with

statins to lower elevated levels of LDL-c, TC, TG, and ApoB in patients with hypercholesterolemia with additive and synergistic effects [39].

However, combination therapy is not completely effective and may be limited because of adverse effects [40]. Although statins are generally well-tolerated in most patients with dyslipidemia, some adverse effects may occur, including myopathy, muscle pain, stiffness, myalgia, and a severe form of rhabdomyolysis. These effects are caused by coenzyme Q deficiency, impaired protein prenylation, oxidative stress, mitochondrial dysfunction, abnormal protein glycosylation, and apoptosis [41, 42]. Rhabdomyolysis, a rare but potentially life-threatening side effect of statins, is caused by the breakdown of skeletal muscle, resulting in the release of the sarcoplasmic proteins AST, ALT, myoglobin, lactate dehydrogenase, aldolase, and creatine kinase as well as electrolytes. It typically presents as myalgia and muscle weakness of the proximal musculature, causing contractile dysfunction and leading to cell damage and muscle cell death [43]. Because of its association with an increased risk of statin-induced myopathy and rhabdomyolysis, the United States Food and Drug Administration does not recommend administering statins at high doses (80 mg/daily) [44]. However, the combined use of statins with other drugs can also increase the risk of rhabdomyolysis because of drug-drug interactions. For example, concurrent therapy with fibrates, primarily fenofibrate, induces rhabdomyolysis compared with monotherapy [45]. Combined therapy with an inhibitor of the enzyme cytochrome P450 3A4 (CYP3A4), which is involved in the oxidation and metabolism of statins, maintains statins longer in the body, thus increasing the risk of adverse effects [46]. Statins are also linked to an increased risk of hepatic dysfunction associated with elevated hepatic transaminase levels, peripheral neuropathy, hyperglycemia, and a risk of incident diabetes [47].

Despite combined therapy, it is difficult to fully engage all therapeutic targets. The pathophysiology of dyslipidemia is likely multifactorial, including heterogeneity and coexisting risk factors [48]. There is still no strategy to evaluate the differential effects of an individual's predisposition to dyslipidemia or comorbidity. In this regard, novel therapeutic modalities as well as appropriate medications and recommendations are needed for patients with dyslipidemia.

Use of THM as a fundamental treatment strategy

THM can serve as an alternative to conventional medicine for the improved management of dyslipidemia owing to its low toxicity and beneficial effects on reducing lipid levels [49, 50]. An important approach to the use of THM is to trace a disease back to the cause of the disease, that is, the internal cause, the external cause, or the cause that is neither internal nor external. Dyslipidemia is a causative factor and risk factor for cardiovascular disease [51]; thus, it is important to prevent and treat dyslipidemia strategically. A discussion of dyslipidemia from the perspective of THM and its fundamental treatment is needed, rather than conventional therapy to simply address the temporary symptoms. According to traditional medicine theory, metabolic syndromes may be categorized into spleen qi (the physical substrate and dynamic force of the functional activities of the spleen) deficiency, qi stagnation (depressed and stagnant flow of qi), dampness obstruction, phlegm, and blood stasis. Depending on the underlying mechanisms of the syndromes, the decoction or treatment method may be varied accordingly [52].

Although the term "dyslipidemia" has not been used in the context of traditional medicine, it is a category of dampness, phlegm, and blood stasis based on the current traditional medicine theory [49] (**Figure 1**), which refers to pathological causes and products resulting from pathologic conditions, such as overeating high-fat diet, dysfunction of transportation, and transformation, impaired digestion, and stagnation [6, 53]. Dampness is an overly wet or moist condition characterized by stickiness, turbidity, heaviness, and a downward trend, which obstructs vital energy. Consequently, it causes symptoms such as high cholesterol, metabolic disorders, chronic fatigue syndrome, cancer, achy joints and limbs, headaches, fibromyalgia, allergies, and various digestive issues. Organically, dampness floods as water and is gathered into phlegm [54]. Phlegm is an endogenous pathological factor that is defined as a viscous, turbid pathological product (such as thick mucus) that accumulates in certain parts of the body, resulting in various diseases [55].

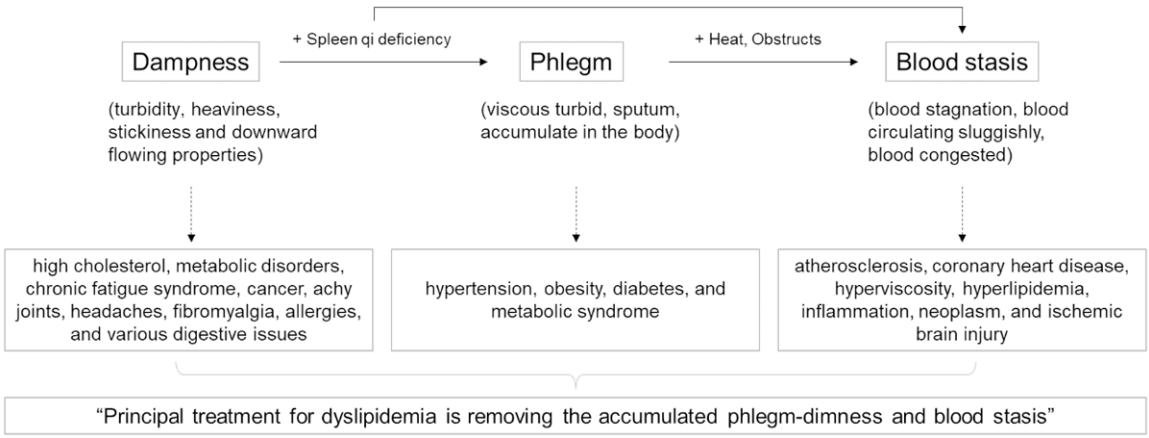

Figure 1. Pathological causes and products of dyslipidemia in traditional medicine theory.

Dampness and phlegm result from an imbalance in body fluid concentration when digestion, transformation, and fluid metabolism are not functioning properly. A constitution study using genomics revealed that phlegm-dampness constitution is susceptible to hypertension, obesity, diabetes, and metabolic syndrome [56]. Another study found altered gut microbiota in obese individuals with phlegm-dampness [57]. Blood stasis is a pathological state of abnormal blood flow in which the circulation is not smooth or becomes stagnant and forms stasis [58]. In a preclinical study, blood stasis was investigated in terms of the early stages of atherosclerosis [59], coronary heart disease [60], hyperviscosity, hyperlipidemia, inflammation, neoplasm, and ischemic brain injury [61].

A deficiency in spleen and kidney function is the basis of dyslipidemia, following disorders of digestion, absorption, transport, and excretion of food, which results in pathological products, such as phlegm, dampness, and blood stasis [6]. It is aggravated by overeating greasy meals, being overweight, a lack of physical activity, and metabolic diseases [49]. Therefore, the principal treatment for dyslipidemia is removal of the accumulated phlegm-dimness and blood stasis and improvement of blood circulation in the body, similar to clearing a pipe to improve clean water flow.

Advantages of THMs for the treatment of dyslipidemia

Phlegm-dampness and blood stasis may be associated with several clinical manifestations, including fever, inflammation, and swelling. There are many options in traditional medicine, including prescriptions, and/or herbal medicine to address these problems. For example, in clinical practice, interior heat-clearing medicines are usually effective in eliminating heat and dampness, which indicates that an interior heat pattern of dyslipidemia may be treated using THM. Plant-derived bioactive compounds with antioxidant and anti-inflammatory properties have been used to protect the vascular endothelium, prevent lipid oxidation, and lower lipid levels. As representative compounds, phenolics and flavonoids from medicinal plants have been reported to be effective [62]. Mitochondria-targeting antioxidants represent a potential strategy for treating nonalcoholic fatty liver disease (NAFLD)-associated liver diseases [15]. Thus, antioxidants may serve as a therapeutic framework for disease treatment.

Another strength of THM is its multicomponent nature. The diversity and complexity of multicomponent THM enable the targeting of alternative pathways and biological processes to treat complex diseases [63]. As mentioned above, dyslipidemia is the consequence of multiple factors; therefore, its clinical manifestations are also complicated, not only in terms of elevated serum lipid levels but also multifarious disorders. In this regard, a holistic approach to treating different conditions is needed; thus, THM can play a key role in the treatment of dyslipidemia [64]. When medicinal herbs are prescribed based on the combination principle, combined herbs can exert beneficial effects as a result of the synergistic interactions of the herb components. Well-established multiherb

combination therapies not only achieve the desired therapeutic outcome but may also decrease undesirable and harmful effects; however, the pharmacokinetic interactions of single or combined medicines remain a major concern [65].

Screening of clinical prescriptions used frequently

We conducted a screening study of 89 clinical prescriptions used frequently on dyslipidemia to identify applicable THMs for dyslipidemia treatment. We found that 17 prescriptions had an inhibitory effect on lipid accumulation when they were administered prior to lipid induction, and 15 prescriptions had an inhibitory effect when they were administered after lipid induction in HepG2 cells compared with atorvastatin-treated cells (**Table 1**). Based on screening for the prescriptions' preventative or curative effects on lipid accumulation, the top three effective prescriptions were selected and are discussed below.

Cheong-sang-bang-pung-san

Cheong-sang-bang-pung-san (CSBPS; "Qing-shang-fang-feng-san" in Chinese and "Seijo-bofu-san" in Japanese) is a well-known traditional herbal prescription for the treatment of purulent inflammation, such as acne, and urticaria. CSBPS was first mentioned in *Wanbinhuichun* and it is also mentioned in *Dongeuibogam* by Heo Jun of the Joseon Dynasty of Korea [66]. It consists of Saposhnikoviae Radix, Forsythiae Fructus, Platycodonis Radix, Angelicae Dahuricae Radix, Scutellariae Radix, Schizonepetae Spica, Cnidii Rhizoma, Gardeniae Fructus, Coptidis Rhizoma, Menthae Herba, Aurantii Fructus Immaturus, and Glycyrrhizae Radix et Rhizoma. Studies have demonstrated the pharmacological effects of CSBPS including antibacterial [67] and anti-lipase activities [68] as well as skin rush in acne patients [69]. CSBPS cleans the heat of the upper energizer (the chest cavity), which is considered the major cause of not only acne, furuncles, and sores but also inflammation. CSBPS resolves toxicity and expels wind, as implied by the name of the prescription "Clear the Upper and Guard the Wind Decoction" [70]. As indicated by the composition of the formulation, CSBPS focuses on the "heat" pattern as a therapeutic target for treating inflammatory skin disease by cooling heat [71] as well as antioxidative stress activity [72].

On-cheong-eum

On-cheong-eum (OCE; "Wen-qing-yin" in Chinese and "Unsei-in" in Japanese), also known as "Cleanse the Top and Relieve Headache Decoction", is a traditional herbal prescription that combines Sa-mul-tang and Hwan-ryun-hae-dok-tang. It consists of Coptidis Rhizoma, Phellodendri Cortex, Scutellariae Radix, Gardeniae Fructus, Rehmanniae Radix, Cnidii Rhizoma, Angelicae Gigantis Radix, and Paeoniae Radix [73]. This prescription was first introduced in *Wanbinhuichun* and has been used to treat abnormal uterine bleeding, restore the menstrual cycle, clear heat, purge pathogenic fire, tonify the blood, and resolve toxins [74]. It is used to treat uterine bleeding resulting from heat and gynecological disorders characterized by heat and blood deficiency. Recently, its use has been extended to other diseases, such as incurable skin diseases [75], atopic dermatitis, eczema, psoriasis vulgaris [76], recurrent aphthous stomatitis, Behcet's disease, and diabetes as well as neurological symptoms [77].

Cheong-sang-gyeon-tong-tang

Cheong-sang-gyeon-tong-tang (CSGTT; "Qing-shang-juan-tong-tang" in Chinese and "Seijo-ken-tsu-to" in Japanese), literally meaning "Cleanse the Top and Pain-alleviating Decoction" was first mentioned in *Jejungshinpyun* as a major prescription for headaches and facial pain [78]. CSGTT dispels wind-heat, ameliorates wind-cold dampness, relieves pain, and purges liver fire against headaches caused by cold, migraine, and tension. It consists of Angelicae Gigantis Radix, Cnidii Rhizoma, Araliae Continentalis Radix, Osterici seu Notopterygii Radix et Rhizoma, Angelicae Dahuricae Radix, Saposhnikoviae Radix, Atractylodis Rhizoma, Liriopis seu Ophiopogonis Tuber, Scutellariae Radix, Chrysanthemi Indici Flos, Viticis Fructus, Asiasari Radix et Rhizoma, Glycyrrhizae Radix et Rhizoma, and Zingiberis Rhizoma Recens. CSGTT plays a role in analgesia, anticonvulsion, and antihyperlipidemia [79]; however, its pharmacological activity has not been studied extensively.

Table 1. Lipid-lowering effect of 89 clinical prescriptions used frequently on HepG2 cell lines

NO.	Prescriptions	Prevention strategy	Treatment strategy
		Reduction rate (%)	Reduction rate (%)
1	Antae-eum	-9	57
2	Baenongsangeup-san	30	42
3	Bangkeehwangkee-tang	-12	47
4	Banhabakchulcheonma-tang	40	33
5	Banhahoo Granule	24	26
6	Banhahubak-tang	28	53
7	Banhasasim-tang	-28	21
8	Bojungikgi-tang	19	22
9	Buhnsimgieum	19	35
10	Bulhwangeumjeonggi-san	15	39
11	Chengsimyeunjaeum	-3	27
12	Cheongsangbangpung-san	49	52
13	Cheongsanggyeontong-tang	34	51
14	Cheonwangbosim-dan	-15	34
15	Chokyungjongok-tang	32	44
16	Chungseoikgi-tang	36	29
17	Daegunjoong-tang	28	50
18	Daehwajung-eum	29	30
19	Daehwangmokdan-tang	27	18
20	Daeshiho-tang	27	35
21	Daeyoung-jeon	18	28
22	Dangguijakyak-san	17	47
23	Dangguiniantong-tang	30	3
24	Dangguisu-san	-18	14
25	Doinseunggi-tang	28	19
26	Dokhwalgisaeng-tang	28	43
27	Eunkyo-san	19	37
28	Galgeun-tang	17	5
29	Gamiondam-tang	24	45
30	Gamisoyo-san	13	10
31	Gumiganghwal-tang	17	19
32	Gungha-tang	17	36
33	Gwakhyangjeonggi-san	-13	-1
34	Gyejibokryeong-hwan	-20	-2
35	Hwanggigunjung-tang	39	28
36	Hwanglyeonhaedok-tang	11	56
37	Hyangsapyeongwi-san	24	16
38	Hyangsayukgunja-tang	-21	16
39	Hyangso-san	15	19
40	Hyeonggaeyeongyo-tang	28	43
41	Hyulbuchukeo-tang	25	48
42	Insamyangyoung-tang	23	51
43	Jaeumganghwa-tang	27	33
44	Jagamcho-tang	32	42
45	Jakyak gamcho-tang	6	12
46	Jihwangeum-ja	-16	53

47	Jodeung-san	25	56
48	Kamiguibitang	26	-3
49	Kumikanghal-tang	10	24
50	Kungkwikyoae-tang	29	11
51	Kyeji-tang	11	24
52	Maekmundong-tang	-41	-3
53	Mahwang-tang	6	27
54	Majain-hwan	-9	29
55	Naeso-san	17	16
56	Ojeok-san	40	33
57	Oncheong-eum	33	53
58	Onkyung-tang	2	-10
59	Oryeong-san	36	26
60	Paljung-san	10	44
61	Palmijihwang-tang	-17	15
62	Palmul-tang	41	27
63	Pyeongwi-san	40	16
64	Saengkangsasim-tang	36	34
65	Saengmaek-san	3	0
66	Samchulgeonbi-tang	31	24
67	Samryeongbaekchul-san	-23	-12
68	Samul-tang	23	15
69	Sanjoin-tang	28	50
70	Sayeoksan	5	23
71	Sikyungbanha-tang	35	28
72	Sipjeondaebo-tang	25	42
73	Siryung-tang	30	51
74	Socheongryong-tang	14	17
75	Sogunjung-tang	28	44
76	Sokyunghwalhul-tang	20	52
77	Sopung-san	26	46
78	Ssanghwa-tang	28	39
79	Taglisodog-eum	34	43
80	Ukgan-sangajinphibanha	31	45
81	Wiryeong-tang	38	30
82	Yeongyechulgam-tang	-2	18
83	Yeonkyopaedok-san	24	35
84	Yijung-tang	38	35
85	Yongdamsagan-tang	17	28
86	Youngseonjaetong-eum	23	52
87	Yukgunja-tang	-12	55
88	Yukmijihwang-tang	40	30
89	Zeolyung-tang	38	22
-	Atorvastatin (20 μM)	32	49

HepG2 cells were cultured in 96-well plates at a density of 5×10^4 cells/well for 24 h. To investigate the preventive effect, cells were incubated with each of the above prescriptions (100 μg/mL) or atorvastatin (20 μM) as a positive control in the presence of a free fatty acid (FFA) mixture (oleic acid/palmitic acid, 2:1 ratio) for 24 h. The following day, the intracellular lipid content was fluorescently measured using AdipoRed reagent at excitation/emission wavelengths of 485/572 nm. For the treatment effect experiment, lipid accumulation was induced in the cells with an FFA mixture for 24 h and then the cells were incubated with each prescription (100 μg/mL) or atorvastatin (20 μM) for a further 24 h. The lipid content was analyzed using AdipoRed reagent according to the manufacturer's protocol.

Screening of single herbal medicines

THMs commonly used to treat dyslipidemia include Salviae Miltiorrhizae Radix, Crataegi Fructus, Alismatis Rhizoma, Atractylodis Rhizoma Alba, Ginkgo, Ganoderma, and Curcumae Longae Rhizoma, which are effective at reducing serum lipid levels [80]. We discovered that most of the listed prescriptions used clinically contain Scutellariae Radix, Alismatis Rhizoma, and Atractylodis Rhizoma Alba. Based on this finding, an optimized herbal medicine was developed and is considered effective for thrombotic disease [81]. Herein, we discuss the properties of each herbal medicine that exhibits antidyslipidemia activity.

Scutellariae Radix

Scutellariae Radix (the dried root of *Scutellariae baicalensis* Georgi) is a perennial herb belonging to the family Lamiaceae. It has a long history of use in traditional medicinal formulations because of its activity in clearing away heat, purging fire, draining dampness, and removing toxins [50]. Scutellariae Radix exhibits a wide range of pharmacological activities, including effects on the nervous and immune systems; liver protection; and antitumor, anti-inflammatory [82-85], antibacterial, and antiviral effects, lipid-lowering, antiobesity [86-88], and antioxidant [89] effects. These therapeutic effects are predominantly induced by flavonoids, the most abundant components of Scutellariae Radix.

The six major bioactive flavones in Scutellariae Radix have been identified. The existing forms include aglycones, such as baicalein, wogonin, and oroxylin A, and glycosides, such as baicalin, wogonoside, and oroxylin A-7-glucuronide. All are pharmacologically active flavones that are useful for treating inflammation, virus-related diseases, and cancers [90]. As predicted, the lipid-lowering component of Scutellariae Radix with the highest activity is the flavonoid compound baicalin and its aglycone baicalein. Baicalin exerts anti-lipidemic [87] and anti-inflammatory activities [91, 92]. Baicalein has strong anti-inflammatory [93], antioxidative [94], antitumor [95], antiobesity [96] activities. It exhibits potent antioxidant, antithrombotic, and anti-inflammatory activities in endothelial cells and antihypertensive effects *in vivo* [97]. Huang *et al.* reported the protective effect of baicalein on cardiovascular disease, suggesting an associated mechanism that can protect against oxidative stress by interfering with apoptosis induced by endoplasmic reticulum stress in cardiomyocytes [98].

Alismatis Rhizoma

Alismatis Rhizoma is derived from the dried stem tuber of *Alisma orientale* (Sam.) Juzep. (Alismataceae). It is used to treat dysuria, edema, hyperlipidemia, nephropathy, and diabetes by promoting diuresis with mechanisms of resolving dampness and expelling heat. Alismatis Rhizoma exhibits multiple pharmacological effects, including antihyperlipidemic [80], antihyperglycemic [99], anti-inflammatory [100-102], hepatoprotective [103], antiobesity [104], and anticancer [105] activities.

A wide range of pharmacologically active compounds, primarily triterpenoids, sesquiterpenoids, and diterpenoids, have been isolated from Alismatis Rhizoma, of which alisols, the protostane-type triterpenoids, are well known for their unique chemical structures with numerous derivatives and various biological activities [106]. Triterpenes are the main active components of Alismatis Rhizoma, which exert hypolipidemic effects by inhibiting cholesterol absorption and synthesis and improving lipid metabolism [50].

Atractylodis Rhizoma Alba

Atractylodis Rhizoma primarily contains *Atractylodes japonica* Koidzumi and *Atractylodes macrocephala* Koidzumi is commonly used as a traditional medicine in East Asia. It is used for the treatment of digestive disorders, diarrhea, rheumatic diseases, systemic edema, bloating, night blindness, and influenza. Previous studies have indicated that Atractylodis Rhizoma Alba exhibits a range of pharmacological activities, including antioxidant [107], antiobesity [108, 109], antidiabetes [110, 111], and anti-inflammatory [112, 113] effects as well as lowering serum lipid levels [80].

It contains a series of sesquiterpenoids, oligosaccharides, polysaccharides, monoterpenes, polyacetylenes, phenolic acids, and steroids that contributes to its beneficial effects [114]. Atractylenolide exhibits various pharmacological effects, including anti-inflammatory [115, 116], antioxidant [117-120], and anticancer

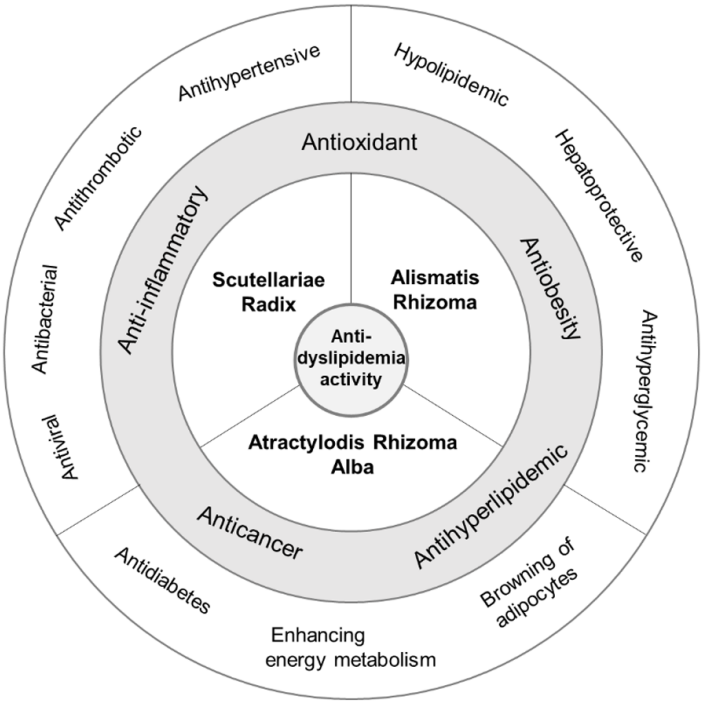

Figure 2. Pharmacological effects of THM related to a potential mechanism of anti-dyslipidemia activity.

[117] activities. In terms of metabolism, atractylenolide enhances energy metabolism [121], modulates farnesoid X receptor receptor [122], improves NAFLD [123], and stimulates the browning of adipocytes [124]. Atractyloside, a diterpenoid glycoside, was shown to exert a therapeutic effect on type 2 diabetes [125] and hepatic steatosis [126] through metabolic regulation.

Discussion

The three selected prescriptions CSBPS, OCE, and CSGTT have been approved by The Korean Ministry of Food and Drug Safety for clinical use. Interestingly, these THM prescriptions have not been traditionally used for obesity or dyslipidemia. This review highlights the role of THM as a potent lipid-lowering treatment with expanded clinical indications. THM may serve as an alternative to Western medications for dyslipidemia treatment. The current literature indicates that a battery of compounds, including terpenoids, saponins, alkaloids, and polyphenols, are derived from THM and have been shown to exert therapeutic effects in metabolic systems. Of these, polyphenols, including flavonoids and tannins, are abundant in many THMs used for treating dyslipidemia. Notably, their protective effects are primarily attributed to their anti-inflammatory, antioxidant, antiobesity, hypolipidemic, and antitumor effects (**Figure 2**) as has been described earlier [80].

Antioxidants are considered potential therapies for treating many illnesses. A significant positive correlation was observed between oxidative stress and dyslipidemia [127]; therefore, enhancing antioxidant supply may prevent or reverse the course of dyslipidemia development. For example, resveratrol is well known for its antioxidant activity in grapes [128], Polygoni Cuspidati Rhizoma et Radix [129], and Mori Fructus [130]. Furthermore, resveratrol inhibits the transcription of PCSK9, including sterol regulatory element-binding protein-2 (SREBP2) and hepatocyte nuclear factor 1α (HNF1α), the PCSK9/LDLR interaction, maturation of PCSK9 in the endoplasmic reticulum, and the secretion of PCSK9 from hepatic cells [131].

Considering the traditional indications of the three prescriptions, they share a mechanism for the control of inflammation and fever by ameliorating heat and pain. Because metabolic disease is associated with low-grade chronic inflammation [132], managing the inflammatory response using THM represents a promising therapeutic strategy for dyslipidemia.

The THM formula consists of a wide variety of ingredients with innumerous chemical molecules, making it possible for THM treatment to exhibit “multiple herbs, multiple target” pharmacological effects [72]. This results in add-on effects not only for certain indications but also for symptoms of the disease. Hence, THMs are expected to have a synergistic effect on dyslipidemia as well as other conditions that are associated with dyslipidemia, although a single herbal medicine also has potential effects on the disease. This suggests an emerging picture of prevention and treatment for a series of diseases, such as hyperlipidemia, hypertension, and arteriosclerosis, through the development

of THM preparations that target metabolic diseases.

Based on current data, it is difficult to identify individual compounds and their molecular targets and completely interpret the observed therapeutic benefits and molecular actions of THM. However, several approaches have been developed, such as systems biology for understanding effects on the cell, tissue, or organism as well as network pharmacology, which is a powerful tool for revealing the complex mechanisms associated with THM [133]. Further studies are needed to elucidate the molecular mechanism underlying the therapeutic effects of THM and to take advantage of the multitarget nature of THM, which may be superior to commercial agents. The precise study of the mechanisms associated with THM will aid in the development of individualized treatment strategies for patients with dyslipidemia.

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Disclosure of conflict of interest

None.

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