

Structurally Diverse Flavonoids from *Citrus medica* L. Var. *sarcodactylis* Swingle and Their Multiple Bioactivities: A Review

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Abstract *Citrus medica* L. var. *sarcodactylis* Swingle is the fruit of *Citrus* L., which belongs to the Rutaceae family. It has the effects of soothing liver and regulating qi, relieving pain in stomach, drying dampness and resolving phlegm in the clinical aspect of traditional Chinese medicine. There are many kinds of chemical components in *C. medica* L. var. *sarcodactylis* Swingle, which mainly including flavonoids, coumarins, alkaloids, volatile oils and other compounds. With the continuous in-depth study of *C. medica* L. var. *sarcodactylis* Swingle at home and abroad, it is gradually determined that flavonoids are the important material basis for its pharmacological effect. In order to further clarify the chemical structure characteristics and pharmacological activities of flavonoids in *C. medica* L. var. *sarcodactylis* Swingle, the chemical components and pharmacological effects of flavonoids reported in recent years are reviewed, which provide reference for the in-depth study of flavonoids in *C. medica* L. var. *sarcodactylis* Swingle.

Keywords: *Citrus medica* L. var. *sarcodactylis* Swingle, flavonoids, chemical components, pharmacological activities

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1. Introduction

Citrus medica L. var. *sarcodactylis* Swingle, named Foshou in Chinese, is the fruit of *Citrus* L., which belongs to the Rutaceae family [1]. It is named because its carpels separate when the fruit is mature and form slender and curved fruit petals like fingers [2]. It is also called five-finger citron, bergamot, five-finger orange, etc [3]. *C. medica* L. var. *sarcodactylis* Swingle is not only used as a delicious fruit, but also served for a traditional Chinese medicine in China. *C. medica* L. var. *sarcodactylis* Swingle tastes pungent, bitter, sour. It is warm in nature and belongs to the liver, spleen, stomach, lung meridians. It has the effects of soothing liver and regulating qi, harmonizing stomach and relieving pain, drying dampness and resolving phlegm. Clinically, it is commonly used to treat liver and stomach qi stagnation, chest and flank pain, epigastric fullness, less food and vomiting, cough and phlegm [4]. It is one of the traditional bulk Chinese

medicinal materials in China. The Pharmacopoeia of the People's Republic of China (hereinafter referred to as the Pharmacopoeia) has been published since 1963, and has been recorded today [5]. In China, *C. medica* L. var. *sarcodactylis* Swingle can be divided into Guang bergamot, Chuan bergamot, Golden bergamot, Jian bergamot according to their origin [6].

Modern research showed that the chemical components in *C. medica* L. var. *sarcodactylis* Swingle were complex and diverse, mainly including flavonoids, coumarins, alkaloids, volatile oils and other components [7-10]. As the main pharmacodynamic component of *C. medica* L. var. *sarcodactylis* Swingle, flavonoids have many pharmacological activities, such as reducing blood lipid, anti-atherosclerosis, anti-oxidant, hypoglycemic, anti-inflammatory and so on [11,12,13]. With the deepening of the research on the pharmacological activities of *C. medica* L. var. *sarcodactylis* Swingle, a dual-purpose Chinese medicine for medicine and food, flavonoids in *C. medica* L. var. *sarcodactylis* Swingle have been gradually taken as the characteristic

components and main active components in recent years. In order to further clarify the chemical structure characteristics and biological activities of flavonoids in *C. medica* L. var. *sarcodactylis* Swingle, this paper summarizes the flavonoids and their pharmacological activities reported in *C. medica* L. var. *sarcodactylis* Swingle at home and abroad in recent years.

2. Phytochemistry

C. medica L. var. *sarcodactylis* Swingle contained many types of chemical components. According to modern research reports, hundreds of chemical components with different structural types such as flavonoids, coumarins, alkaloids and volatile oils have been isolated and identified from *C. medica* L. var. *sarcodactylis* Swingle. Flavonoids are not only regarded as the characteristic components of *C. medica* L. var. *sarcodactylis* Swingle, but also determined as the main active components of traditional Chinese medicine of *C. medica* L. var. *sarcodactylis* Swingle [14]. It is common knowledge that flavonoids mainly come from the synthesis of cinnamic acid. According to the structural characteristics of flavonoids in *C. medica* L. var. *sarcodactylis* Swingle, they are roughly divided into flavonoids, flavonols, and dihydroflavonoids. Among them, flavonoids are the largest proportion of these compounds. According to the chemical structure and biogenic pathway of flavonoids, they are divided into flavonoid glycosides and flavonoid aglycones. Meanwhile, these compounds in *C. medica* L. var. *sarcodactylis* Swingle can be divided into O-glycosides and C-glycosides according to the different types of glycoside bonds in flavonoid glycosides.

2.1. Flavonoid and Dihydroflavonoid Glycosides

Flavonoid and dihydroflavonoid glycosides are two kinds of natural organic compounds widely existing in

nature. Most of these compounds exist in plants in the form of glycosides. There are many kinds of flavonoid aglycones, which are mainly formed by oxidation (including hydrogen oxidation and methyl oxidation) at the main position of the basic skeleton of flavonoids. Sugar substituents are mostly connected with the carbon skeleton of flavonoids in the form of hydrogen oxidation to form O-glycosides, or directly connected with the C atom on the benzene ring to form C-glycosides. It is found that flavonoid glycosides are an important chemical component in *C. medica* L. var. *sarcodactylis* Swingle. The structural characteristics of these components are that flavonoid glycosides are condensed with monosaccharides or disaccharides to obtain the corresponding flavonoid glycosides according to relevant references. These compounds are divided into flavone-O-glycosides, dihydroflavone-O-glycosides and flavone-C-glycosides according to the type of glycoside bond. It is found that flavonoid glycosides are an important chemical component in *C. medica* L. var. *sarcodactylis* Swingle.

2.2. Flavone-O-glycosides

Up to now, eight flavone-O-glycosides have isolated from *C. medica* L. var. *sarcodactylis* Swingle by researchers at home and abroad. Among them, there are one flavone monoglycoside, five flavone diglycosides, two flavone triglycosides. The connection positions of these sugars are mainly distributed at C-7, and the connection mode of disaccharides is 3- α -L-arabinopyranosyl-(1 $\rightarrow$ 3)-galactoside. These compounds are determined as scutellarein 4'-methyl ether 7-O-glucuronide (1) [15], limocitrol 3- α -L-arabinopyranosyl-(1 $\rightarrow$ 3)-galactoside (2) [16], diosmetin 7-O-neohesperidoside (3) [17], apigenin 7-O-neohesperidoside (4) [17], diosmin (5) [18], chrysoeriol 7-O-neohesperidoside (6) [17], chrysoeriol 7-O-neohesperidoside-4'-glucoside (7) [17], apigenin 7-O-neohesperidoside-4'-glucoside (8) [17]. The related information of flavonoid glycosides (1-8) is shown in Table 1 and Figure 1.

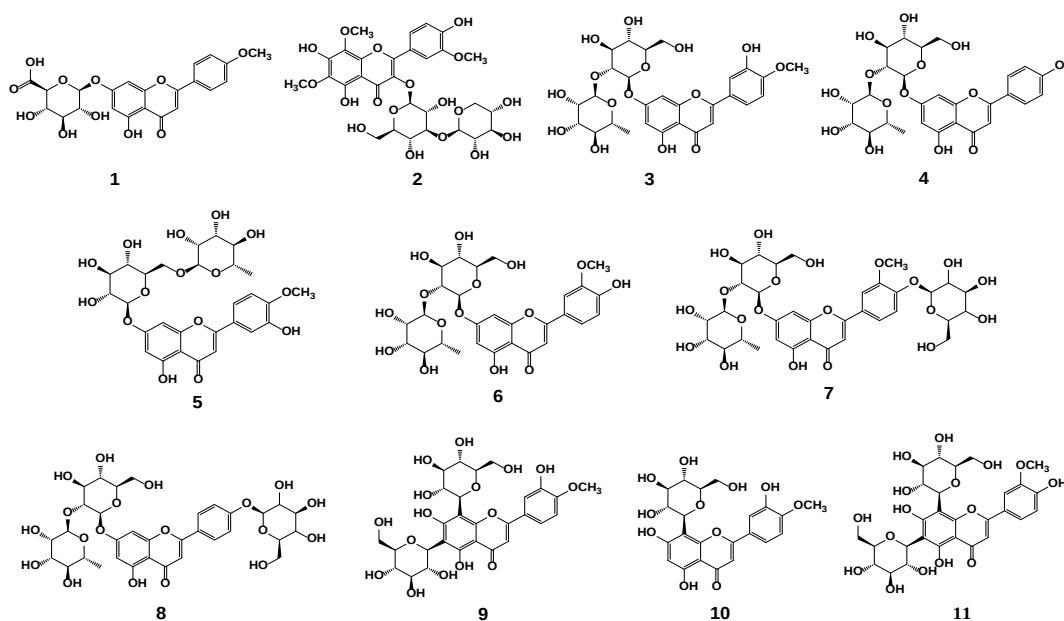
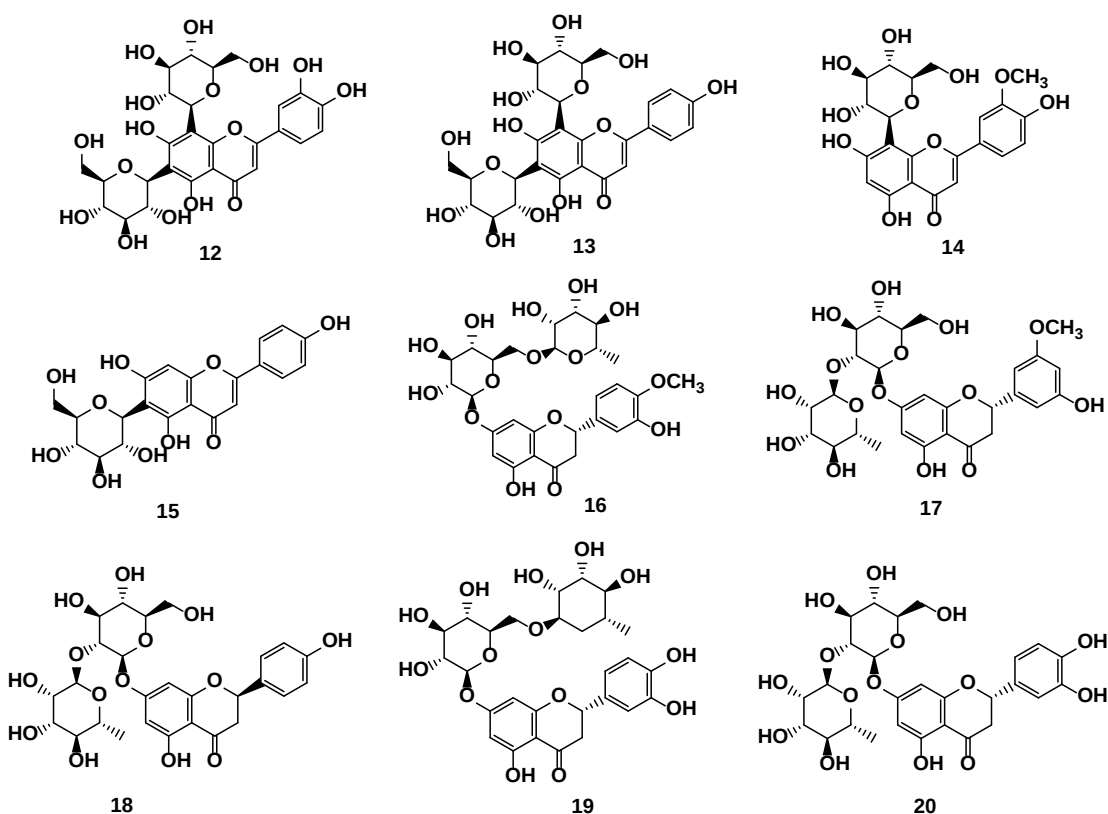


Figure 1. Structures of flavonoid glycosides (1-11) from *C. medica* L. var. *sarcodactylis* Swingle

Table 1. Flavonoid and dihydroflavonoid glycosides (1-20) were isolated from *Citrus medica* L. var. *sarcodactylis* Swingle.

No.	Name	Type	Formula	Reference
1	scutellarein 4'-methyl ether 7-O-glucuronide	flavone-O-glycoside	C ₂₂ H ₂₀ O ₁₁	[15]
2	limocitrol 3- α -L-arabinopyranosyl-(1->3)-galactoside	flavone-O-glycoside	C ₂₉ H ₃₄ O ₁₈	[16]
3	diosmetin 7-O-neohesperidoside	flavone-O-glycoside	C ₂₈ H ₃₂ O ₁₅	[17]
4	apigenin 7-O-neohesperidoside	flavone-O-glycoside	C ₂₇ H ₃₀ O ₁₄	[17]
5	diosmin	flavone-O-glycoside	C ₂₈ H ₃₂ O ₁₅	[18]
6	chrysoeriol 7-O-neohesperidoside	flavone-O-glycoside	C ₂₈ H ₃₂ O ₁₅	[17]
7	chrysoeriol 7-O-neohesperidoside-4'-glucoside	flavone-O-glycoside	C ₃₄ H ₄₂ O ₂₀	[17]
8	apigenin 7-O-neohesperidoside-4'-glucoside	flavone-O-glycoside	C ₃₃ H ₄₀ O ₁₉	[17]
9	diosmetin-6,8-di-C-glucoside	flavone-C-glycoside	C ₂₈ H ₃₂ O ₁₆	[17]
10	diosmetin-8-C-glucoside	flavone-C-glycoside	C ₂₂ H ₂₂ O ₁₁	[17]
11	chrysoeriol 6,8-di-C-glucoside	flavone-C-glycoside	C ₂₈ H ₃₂ O ₁₆	[17]
12	luteolin 6,8-di-C-glucoside	flavone-C-glycoside	C ₂₇ H ₃₀ O ₁₆	[17]
13	apigenin 6,8-di-C-glucoside	flavone-C-glycoside	C ₂₇ H ₃₀ O ₁₅	[17]
14	chrysoeriol 8-C-glucoside	flavone-C-glycoside	C ₂₂ H ₂₂ O ₁₁	[17]
15	apigenin 6-C-glucoside	flavone-C-glycoside	C ₂₁ H ₂₀ O ₁₀	[17]
16	hesperidin	dihydroflavone-O-glycoside	C ₂₈ H ₃₄ O ₁₅	[18]
17	neohesperidin	dihydroflavone-O-glycoside	C ₂₈ H ₃₄ O ₁₅	[19]
18	naringin	dihydroflavone-O-glycoside	C ₂₇ H ₃₄ O ₁₂	[20]
19	eriocitrin	dihydroflavone-O-glycoside	C ₂₇ H ₃₂ O ₁₅	[19]
20	neeriocitrin	dihydroflavone-O-glycoside	C ₂₇ H ₃₂ O ₁₅	[20]

**Figure 2. Structures of flavonoid glycosides and dihydroflavonoid glycosides (12-20) from *Citrus medica* L. var. *sarcodactylis* Swingle**

2.3. Flavone-C-glycosides

It was found that five flavone-C-glycosides were isolated from *C. medica* L. var. *sarcodactylis* Swingle. By analyzing their structures, it was found that the type of sugar connected to these compounds was glucose, and the connecting positions of glucose were mostly C-6 or C-8. These compounds are elucidated as: diosmetin-6,8-di-C-glucoside (9) [17], diosmetin-8-C-glucoside (10) [17],

chrysoeriol 6,8-di-C-glucoside (11) [17], luteolin 6,8-di-C-glucoside (12) [17], apigenin 6,8-di-C-glucoside (13) [17], chrysoeriol 8-C-glucoside (14) [17], apigenin 6-C-glucoside (15) [17]. Among them, C-6 and C-8 of compounds 9, 11, 12, 13 are connected with two glucoses. C-8 of compounds 10 and 14 were connected with one glucose. C-6 of compound 15 was connected with one glucose. The related information of flavone-C-glycosides (9-15) is shown in Table 1 and Figure 1 - Figure 2.

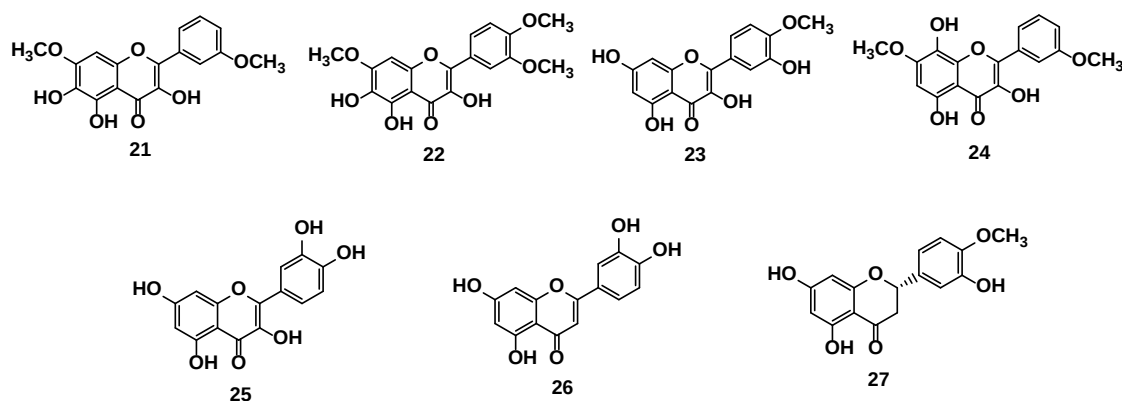


Figure 3. Structures of flavonol, flavonoid, and dihydroflavonoid aglycones (21-27) from *Citrus medica* L. var. *sarcodactylis* Swingle

Table 2. Flavonol, flavonoid, and dihydroflavonoid aglycones were isolated from *Citrus medica* L. var. *sarcodactylis* Swingle

No.	Name	Type	Formula	Reference
21	3,5,6-trihydroxy-4',7-dimethoxyflavone	flavonol aglycone	C ₁₇ H ₁₄ O ₇	[21]
22	3,5,6-trihydroxy-3',4',7-dimethoxyflavone	flavonol aglycone	C ₁₈ H ₁₆ O ₈	[21]
23	diosmetin	flavonol aglycone	C ₁₆ H ₁₂ O ₇	[22]
24	3,5,8-trihydroxy-7,4' - dimethoxyflavone	flavonol aglycone	C ₁₇ H ₁₄ O ₇	[23]
25	quercetin	flavonol aglycone	C ₁₅ H ₁₀ O ₇	[24]
26	luteolin	flavonoid aglycone	C ₁₅ H ₁₀ O ₆	[24]
27	hesperetin	dihydroflavone aglycone	C ₁₆ H ₁₄ O ₆	[25]

2.4. Dihydroflavone-O-glycosides

It was found that there were relatively few dihydroflavone-O-glycosides isolated from *C. medica* L. var. *sarcodactylis* Swingle. At present, five dihydroflavone-O-glycosides have been isolated and identified from the plant. Further analysis found that the sugars connected to these compounds are rutinose, and the connection position is generally at position C-7. These compounds are determined as hesperidin (16) [18], neohesperidin (17) [19], naringin (18) [20], eriocitrin (19) [19], neoeriocitrin (20) [20]. The related information of flavone-C-glycosides (16-20) is shown in Table 1 and Figure 2.

2.5. Flavonol, Flavonoid, and Dihydroflavonoid Aglycones

At present, there were three types of aglycones isolated from *C. medica* L. var. *sarcodactylis* Swingle mainly, which included the types of flavonol, flavonoid, and dihydroflavonoid. These compounds are identified as: 3,5,6-trihydroxy-4',7-dimethoxyflavone (21) [21], 3,5,6-trihydroxy-3',4',7-dimethoxyflavone (22) [21], diosmetin (23) [22], 3,5,8-trihydroxy-7,4' - dimethoxyflavone (24) [23], quercetin (25) [24], luteolin (26) [24], hesperetin (27) [25]. Among them, compounds (21-25) are flavonol aglycones. Compounds 26 and 27 are flavonoid aglycone and dihydroflavonoid aglycone, respectively. Further structural analysis showed that C-5 was often substituted by hydroxyl and C-7 was often substituted by hydroxyl or methoxy. C-3' and C-4' are often replaced by hydroxyl or methoxy groups. The related information of flavonol, flavonoid, and dihydroflavonoid aglycones (21-27) is shown in Table 2 and Figure 3.

3. Pharmacological Activity

At present, the research on the pharmacological activity of *C. medica* L. var. *sarcodactylis* Swingle by researchers at home and abroad has gradually shifted from medicinal materials to the effective parts and components, from simple activity screening to mechanism exploration and target confirmation, which gradually determined that the main active components of *C. medica* L. var. *sarcodactylis* Swingle are flavonoids. Flavonoids are widely distributed in the plant world. Most of the compounds structure take 2-phenyl-chromone as the mother core exist in the form of C₆-C₃-C₆, and most of them have significant and special biological activities. They are often effective components in Chinese herbal medicine. Flavonoids, as the characteristic components of *C. medica* L. var. *sarcodactylis* Swingle, have been reported on their pharmacological activities at home and abroad.

3.1. Hypolipidemic and Anti-atherosclerotic Activity

Gong Zheng [26] et al used hyperlipidemia rabbit model to study the effect and mechanism of flavonoids from *C. medica* L. var. *sarcodactylis* Swingle on serum lipids and arteriosclerosis related risk factors. Rabbits of control group were fed with normal food, the other groups were fed with high fat food, and rabbits of flavonoids from *C. medica* L. var. *sarcodactylis* Swingle and fluvastatin group were intragastrically administrated with corresponding drug at dose of 100 mg/kg and 10 mg/kg daily, respectively. The serum TC, TG, IDL-C, HDL-C, NO, MDA, IL-1 β were measured after 10 weeks, as

well as AopE in liver was tested by western blotting. Compared with the control group, the levels of TC and LDL-C in model group were significantly increased ($P<0.05$). Compared with the model group, the levels of TC, LDL-C, TDA, IL-1 β in total flavonoids from *C. medica* L. var. *sarcodactylis* Swingle group were significantly decreased ($P<0.05$), while the NO and the expression of AopE protein in liver tissue were significantly increased ($P<0.05$), the effect of this group was comparable with the fluvastatin group ($P>0.05$). Consequently, the total flavonoids from *C. medica* L. var. *sarcodactylis* Swingle can inhibit hyperlipidemia and atherosclerosis.

It was found that flavonoids in *C. medica* L. var. *sarcodactylis* Swingle could increase the concentration of NO in serum of hyperlipidemia rabbits, suggesting that flavonoids in *C. medica* L. var. *sarcodactylis* Swingle can protect vascular endothelium, promote the recovery of vasodilation function, and antagonize the endothelial damage of atherosclerosis [27].

Modern research exhibited that *C. medica* L. var. *sarcodactylis* Swingle juice had hypolipidemic effects and its protective effect on liver of hyperlipidemic rats [28]. Chronic administration of *C. medica* L. var. *sarcodactylis* Swingle (1 mL/rat/day) provoked a significant reduction in serum cholesterol, triglycerides, low-density lipoprotein (LDL) levels and an increase in high-density lipoprotein (HDL) levels. Moreover, histopathological observations showed a protection of hepatic parenchyma. In addition, fecal neutral sterols and fecal bile acid excretion were found to be increased after *C. medica* L. var. *sarcodactylis* Swingle treatment. These results suggested that the hypocholesterolemic effect of *C. medica* L. var. *sarcodactylis* Swingle might be mediated by the increase in fecal neutral sterols and total bile acids excretion. In addition to the hypolipidemic effect, the juice of *C. medica* L. var. *sarcodactylis* Swingle showed radical scavenging activity in the diphenylpicrylhydrazyl assay, probably may be a connection between these two aspects. These observations suggested that the positive intake of *C. medica* L. var. *sarcodactylis* Swingle reduced the risk of some cardiovascular diseases through its radical scavenging function and hypocholesterolemic action. In conclusion, the research results indicated that *C. medica* L. var. *sarcodactylis* Swingle juice reduced diet-induced hyperlipidemia in rats. It significantly lowered the concentration of serum cholesterol, triglycerides, LDL and elevated the serum HDL level. This hypocholesterolemic effect might be related both a radical scavenging activity and an increase of fecal neutral sterols and total bile acids excretion. Therefore, *C. medica* L. var. *sarcodactylis* Swingle could be considered a valuable supplement to prevent hyperlipidemia diseases.

It was found that secretion of hepatocyte apolipoprotein B (ApoB) was inhibited by the flavonoids, naringenin and hesperetin, via reduced activity and expression of ACAT2 and MTP [29]. In this study, the ability of these flavonoids to modulate ApoB secretion and cellular cholesterol homeostasis was determined in the human hepatoma cell line (HepG2). Decreased ApoB secretion was associated with reducing cellular cholesteryl ester mass. Cholesterol esterification was decreased, dose-dependently, up to 84% ($P<0.001$) at flavonoid concentrations of 200 μ M. Neither

flavonoid demonstrated selective inhibition of either form of acyl CoA: cholesterol acyltransferase (ACAT) as determined using CHO cells stably transfected with either ACAT1 or ACAT2. Additionally, naringenin and hesperetin decreased both the activity and expression of microsomal triglyceride transfer protein (MTP). Both flavonoids caused a 5-fold to 7-fold increase in low density lipoprotein (LDL) receptor mRNA, which resulted in a 1.5-fold to 2-fold increase in uptake and degradation of I-LDL. It was concluded that both naringenin and hesperetin decrease the availability of lipids for assembly of ApoB-containing lipoproteins, an effect mediated by reducing activities of ACAT1 and ACAT2, decreasing in ACAT2 expression, reducing MTP activity. Together with an enhanced expression of the LDL receptor, these mechanisms may explain the hypocholesterolemic properties of the citrus flavonoids.

3.2. Anti-oxidant Activity

Huang Xiaomei [30] et al extracted flavonoids from *C. medica* L. var. *sarcodactylis* Swingle by microwave and ultrasonic method. The optimum parameters were obtained by optimizing the macroporous resin and the concentration of eluent. D101 was selected to separate and purify the crude flavonoids of *C. medica* L. var. *sarcodactylis* Swingle by gradient elution with petroleum ether, water and ethanol. The purity of the purified flavonoids was 92.65%. A comparative study was made on the anti-oxidant activity of V_c , rutin, crude flavonoids and purified flavonoids from *C. medica* L. var. *sarcodactylis* Swingle. The scavenging rates of DPPH $\cdot$ and $\cdot$ OH were 82.22% and 69.46% from purified flavonoids of *C. medica* L. var. *sarcodactylis* Swingle. The results showed that the purified flavonoids from *C. medica* L. var. *sarcodactylis* Swingle had better scavenging ability and stronger anti-oxidant activity.

In 2018, Jin Wang [31] et al extracted flavonoids from *C. medica* L. var. *sarcodactylis* Swingle by ethanol reflux method. Based on the single factor experiments and the indexes of extraction rate, the response surface methodology was employed to optimize the extraction conditions of flavonoids from *C. medica* L. var. *sarcodactylis* Swingle and its anti-oxidant activity was evaluated. The results showed that the optimal extraction conditions of flavonoids from *C. medica* L. var. *sarcodactylis* Swingle were as follows: the ethanol concentration is 73%, extraction temperature is 80°C, extraction time is 90 min, solid-liquid ratio of 1:31 g/mL. Under these conditions, the yield of flavonoids was 1.34%. The results of anti-oxidation experiments showed that flavonoids of *C. medica* L. var. *sarcodactylis* Swingle had certain clearance effect on scavenging DPPH and ABTS free radical, and showed obvious dose-effect relationship, and the scavenging effect on DPPH radical and ABTS with IC_{50} of 0.8 mg/mL and 0.07 mg/mL respectively. And the ORAC (total anti-oxidant capacity) was 20.18 μ mol TE/g. The above results indicated that flavonoids from *C. medica* L. var. *sarcodactylis* Swingle were a good natural antioxidant.

In order to study the ultrasonic extraction technology and anti-oxidant activity of total flavonoids from *C. medica* L. var. *sarcodactylis* Swingle, Huang Jing [32]

et al determined the optimal extraction process of total flavonoids from *C. medica* L. var. *sarcodactylis* Swingle by orthogonal experiment. The scavenging effect of *C. medica* L. var. *sarcodactylis* Swingle flavonoids on $\cdot\text{OH}$ and $\text{O}_2^{\cdot-}$ are obvious and effective, but the anti-oxidant activity is weaker than that of V_C . When the solubility of *C. medica* L. var. *sarcodactylis* Swingle flavonoids is 1.4 mg/mL, the scavenging rate is 54.4% and 39.2%, respectively.

Wang Jin [33] evaluated the anti-oxidant activity of flavonoids from *C. medica* L. var. *sarcodactylis* Swingle *in vitro* by DPPH radical scavenging capacity, ABTS radical scavenging capacity, and total anti-oxidant capacity (ORAC). The results showed that the flavonoids from *C. medica* L. var. *sarcodactylis* Swingle had good anti-oxidant activity *in vitro* before and after purification. From the experimental results, the flavonoids before and after purification could reduce the content of ROS, increase the activity of SOD and CAT and decrease the content of MDA in nematodes, which was consistent with the results under normal culture conditions. Therefore, improving the ability of oxidative stress may be one of the anti-oxidant mechanisms of flavonoids.

3.3. Hypoglycemic Activity

It was found that hesperidin, the main ingredient in *C. medica* L. var. *sarcodactylis* Swingle, could improve the insulin resistance index of type 2 diabetes. Hesperidin can significantly increase the glucose consumption of hepatocytes, regulate up the phosphorylation level of glucose and lipid metabolism related protein AMPK and lipid synthesis key protein ACC, and synergistically reduce the fat accumulation and triglyceride level in hepatocytes modeled by free fatty acids, suggesting that hesperidin can reduce the level of blood glucose and blood lipid, and its concentration is much lower than that of positive drug metformin. It can be used as auxiliary drugs or health products for the prevention and treatment of diseases related to abnormal glucose and lipid metabolism [34].

3.4. Other Activity

Modern studies have found that hesperidin is an important flavonoid with a large content in *C. medica* L. var. *sarcodactylis* Swingle. It is the main component of V_p . It is regarded as the main index component for quality control of bergamot in Chinese Pharmacopoeia (2010 Edition). It has the effects of maintaining osmotic pressure, enhancing capillary toughness, shortening bleeding time, reducing cholesterol [25]. In addition, hesperidin also has strong anti-inflammatory activity, and its mechanism may participate in the role of oxidoreductase *in vivo*, affect the activity of thyroid and prevent adrenaline from oxidation [35].

4. Discussion

This review summarized information on the structure and bioactivity of flavonoids from *C. medica* L. var. *sarcodactylis* Swingle. Collectively, *C. medica* L. var.

sarcodactylis Swingle is a valuable traditional Chinese medicine and worthy of investigating its medicinal aspect. This highly compact summarization in the present review could launch a bridge for the ongoing scientific studies and supply researchers with new direction. We believe that this review can be of particular value by providing fundamental insights into the medicinal value of this plant. Moreover, this review can provide a reference for clinical medication, sustainable development and utilization of this plant.

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Conflict of Interests

The authors declare that they have no conflicts of interest.

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