RSC Advances

REVIEW

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2021, **11**, 31235

A review on the phytochemistry and pharmacology of the herb *Scoparia dulcis* L. for the potential treatment of metabolic syndrome

Zikang Jiang, *[a] Jinghui Sung,[a] Xuyun Wang,[b] Yangyang Zhang,[c] Yaomiao Wang,[a] Haifeng Zhou[a] and Lei Wen *[a]

Received 1st July 2021
Accepted 11th September 2021

DOI: 10.1039/d1ra05090g

rsc.li/rsc-advances

This review discusses the chemical constituents and pharmacological effects of *Scoparia dulcis* L. (*S. dulcis*) plants. So far, approximately 160 compounds have been identified from *S. dulcis*, among which 115 compounds may be related to the treatment of metabolic syndrome. Extracts of *S. dulcis* have effects of reducing fasting blood glucose level, increasing the plasma insulin level, and stimulating insulin secretion to treat diabetes. They also produce antihyperlipidemic effects by increasing serum high-density lipoprotein levels, the anti-atherogenic index of plasma, and HMG-CoA reductase activity. The chemical composition of glutinol and glutinone, isolated from *S. dulcis*, provide potential anti-inflammatory effects. These compounds can also reduce total cholesterol, triacylglycerol, and low-density lipoprotein (LDL)-cholesterol and increase high-density lipoprotein (HDL)-cholesterol to provide the anti-atherosclerotic effect. *S. dulcis* exerts anti-arthritic properties through its effect on cytokine levels, significantly reducing IFN-γ and IL-6 levels and elevating IL-10 levels. The extracts carry out hepatoprotective effect by preventing the descent of the antioxidative enzymes of superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GRd), and glutathione-*S*-transferase (GST). Therefore, *S. dulcis* provides new potential for medicine given its numerous therapeutic properties and can be promoted as a complementary or alternative therapy for patients with chronic conditions.

Introduction

Scoparia dulcis L. (*S. dulcis*) is a medicinal botanical herb that has been widely used for generations in southern China, India, Brazil, Paraguay, and Nigeria. Traditional Chinese medicine believes that *S. dulcis* has stomachic, diuretic, antitussive, heat clearing, and toxin absorbing effects. It is applied in traditional Chinese herbal medicine to treat colds, fever, coughs with lung heat, sore throats, enteritis, abnormal urination, hunger swelling, eczema, and miliaria since ancient times. *S. dulcis* is also commonly used in herbal tea for health benefits in southern China. In other ethnomedicine communities, *S. dulcis* is also used to treat gastric problems, edema, liver diseases, and respiratory diseases.[1] Chemical analysis of *S. dulcis* identified various components including nitrogen-containing compounds, flavonoids, diterpenoids, triterpenoids, steroids, phenolics, and aliphatics, which can demonstrate its definite pharmacological effects. As a result, a large number of researchers started to study the chemical components and pharmacological activities through different extract methods from *S. dulcis* and confirmed that *S. dulcis* provides various pharmacological effects, related to the treatment of metabolic syndrome. These include antidiabetic, anti-hyperlipidaemia, anti-inflammatory, anti-atherosclerotic, anti-arthritic, hepatoprotective, anti-oxidative, and anti-urolithiasis[94] activities. The incidence of metabolic syndrome in the world has been gradually increasing, especially in some developing countries, is even higher than some developed countries.[2] Thus, the chemical substance basis of and current pharmacological research on *S. dulcis* will be comprehensively reviewed to explain its potential role in the treatment of metabolic syndrome. In addition to complementing the use of conventional drugs, some common herbs can guide new drug discoveries, which are also important developments in this field. Therefore, the updated and comprehensive review of the phytochemical and pharmacological properties of *S. dulcis* will provide the foundation for the potential development of new medicine in the treatment of metabolic syndrome.

Methodology and aim of the review

This literature collection on *S. dulcis* was conducted mainly with the SciFinder covering the period from 2000 to 2020. The other electronic sources used were from scientific databases,

[a]*Department of Traditional Chinese Medicine, School of Medicine, Xiamen University, Xiamen, 361102, Fujian Province, China. E-mail: zikangjiang@foxmail.com; wenlei@xmu.edu.cn*

[b]*Department of Andrology, Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, Beijing, 100010, China*

[c]*School of Pharmaceutical Science, Xiamen University, Xiamen, 361102, Fujian Province, China*

including PubMed, ScienceDirect, Web of Science, Google Scholar, Baidu Scholar, Bing academic, ResearchGate, and CNKI. The local literature of traditional Chinese medicine such as Fujian folk herbal medicine, Records of traditional Chinese medicine in Guangxi, Folk herbal medicine in Southern Fujian, Chinese herbal medicine in Guangxi, Manual of commonly used Chinese herbal medicines by Guangzhou Army, Chinese Materia Medica, National collection of Chinese herbal medicines, and Chinese herbal medicine in Fujian, were referenced as well.

To date, there is little literature reviewing the phytochemical and pharmacological basis of *S. dulcis* for the treatment of metabolic syndrome. Previous review article of Mishra *et al.*[3] had briefly introduced some chemical constituents and pharmacological effects of *S. dulcis*. However, the article does not describe the correlation between the various pharmacological actions in detail. In the literature review of Pamunuwa *et al.*,[4] the authors mainly introduced the therapeutic effect of *S. dulcis* on diabetes and only briefly mentioned the other pharmacological effects of *S. dulcis*.

This review article was mainly focused on the treatment of metabolic syndrome to investigate the relevant medical chemistry and pharmacological mechanisms of *S. dulcis*. At the same time, the related pharmacological effects and mechanisms confirmed *in vivo* and *in vitro* experiments can also provide inspiration for the pharmaceutical industry and food supplement to develop the potential medicine or food to treat the metabolic syndrome.

Chemical constituents

There are 115 compounds in *S. dulcis* that have therapeutic potential for the treatment of metabolic syndrome. The chemical structures of compounds in *S. dulcis* are listed in the following section. These chemical substances can be roughly divided into the following categories: nitrogen-containing compounds, flavonoids, diterpenoids, triterpenoids, steroids, phenolics, and other aliphatics. So far, the flavonoids, diterpenoids, and alkaloids contained in *S. dulcis* are the most diverse. Each of the compounds has been marked with a number (1–115), and some of them have defined unique biological activities. The antidiabetic, hypolipidemic, anti-inflammatory, and antioxidative effects of these compounds are the molecular basis for the use of *S. dulcis* in the treatment of metabolic syndrome. The compounds are extracted from different parts of *S. dulcis*, including the whole plant, aerial parts, leaves, and roots. Most of the compounds are isolated from the leaves of *S. dulcis*. The pharmacological activities of some compounds need to be further studied, and some compounds are expected to be further researched and developed as medicines for the treatment of metabolic syndrome.

Nitrogen-containing compounds

Nitrogen containing compounds, of which alkaloids are the most important, are very commonly found in plants. In recent years, studies have found that some benzoxazin-3-one derivatives can act as mineralocorticoid receptor antagonists to treat hypertension, thereby treating some cardiovascular diseases.[5] 2-hydroxy-2*H*-1,4-benzoxazol-3-one in *S. dulcis* was discovered by Kamperdick *et al.*[6] Benzoxazine and benzoxazolinone were reported by Babincova *et al.*[7] and Mishra *et al.*[3] Coixol, 1-hydroxy-6-methoxy-2-benzoxazolinon, 3,6-dimethoxy-benzoxazolin-2(3*H*)-one, (2*R*)-2-(β-D-glucopyranosyloxy)-7-methoxy-2*H*-1,4-benzoxazin-3(4*H*)-one, (2*R*)-2-(β-D-glucopyranosyloxy)-4,7-dimethoxy-2*H*-1,4-benzoxazin-3(4*H*)-one, and (2*R*)-7-methoxy-2*H*-1,4-benzoxazin-3(4*H*)-one 2-*O*-β-galactopyranoside were isolated from the water extract of the dried aerial parts of *S. dulcis* by Wu *et al.*[8] Dextromoramide and 2-heptadecyl-2-imidazoline were identified in the methanol extract and 1-methyl-2-pyrrolidinone, N^1-acetylspermine, cyclohexylamine, and procaine were identified in the water extract of *S. dulcis* by Wankhar *et al.*[9] Tin *et al.*[10] investigated the methanol fraction of whole plants of *S. dulcis* and isolated 2-hydroxy-7-methoxy-1,4(2*H*)-benzoxazin-3-one 2-*O*-β-D-glucopyranoside. In addition, two catecholamines, epinephrine and norepinephrine, were identified in the aqueous extract of *S. dulcis* by Freire *et al.*[11] Epinephrine and norepinephrine act on α and β receptors, to accelerate heart rate and raise blood pressure. The chemical structures of the nitrogen-containing compounds are shown in Table 1.

Flavonoids

Flavonoids are one of the most important compounds in *S. dulcis*. Flavonoids generally refer to a series of compounds composed of two benzene rings (A ring and B ring) with phenolic hydroxyl groups connected to each other through three central carbon atoms, creating a compound composed of C_6–C_3–C_6 units. So far, the flavonoids in *S. dulcis* can be roughly divided into flavones, flavonols, flavan-3-ols, and flavanones.

Flavones

According to the current literature research, most of the flavonoids found in *S. dulcis* are flavones. Scutellarin methylester, cynaroside, 5,7,8,3′,4′,5′-hexahydroxy-flavone glucuronide, and 5-hydroxy-6,7-dimethoxyflavone-4′-*O*-β-glucose were isolated from *S. dulcis* by Kawasaki *et al.*[12] 5,7,8,3′,4′,5′-hexahydroxy-flavone glucuronide and *iso*-vitexin showed β-glucuronidase inhibitory activity in the experiments.[12] In the same year, Hayashi *et al.*[13] used 70% ethanol to extract the above-ground parts of *S. dulcis*, and isolated 5,7-dihydroxy-3′4′,6,8-tetrametoxyflavone from it. This compound exhibited significant cytotoxic activity against HeLa 299 and S3 cell lines with ID_{50} values of 0.097 and 0.140, respectively. Three flavone glycosides, 5,6,4′-trihydroxyflavone 7-*O*-α-L-2,3-di-*O*-acetylrhamnopyranosyl-(1→6)-β-D-glucopyranoside, apigenin 7-*O*-α-L-2,3-di-*O*-acetylrhamnopyranosyl-(1→6)-β-D-glucopyranoside, and apigenin 7-*O*-α-L-3-*O*-acetylrhamnopyranosyl-(1→6)-β-D-glucopyranoside were isolated from methanol extract of *S. dulcis* for the first time.[14] The latter two compounds have been experimentally confirmed to have the effect of promoting NGF-induced neurite outgrowth in PC12D cells. Acacetin, cirsimarin, cynaroside, linarin, vicenin-2, vitexin, and *iso*-vitexin were reported by Mishra *et al.*[3] and some of them have antioxidative and hypotensive activities. Liu *et al.*[15] determined

Table 1 The chemical structures of nitrogen-containing compounds, extracted from various part of *S. dulcis*

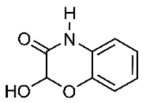
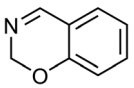
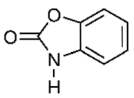
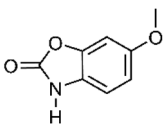
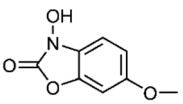
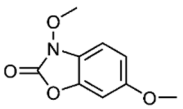
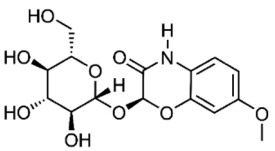
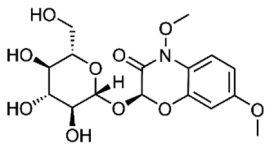
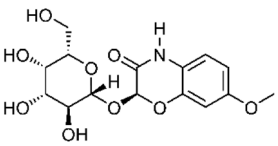
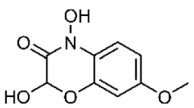
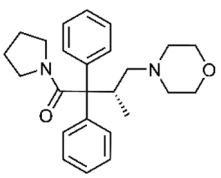
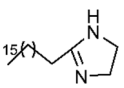
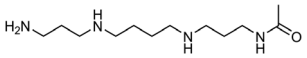
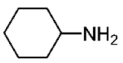
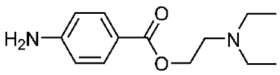
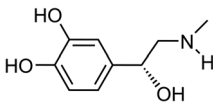
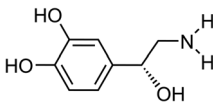
No.	Compound	Part of plant	Chemical structure	CAS number	Chemical formula	Ref.
1	2-Hydroxy-2*H*-1,4-benzoxazol-3-one	Whole plant			$C_8H_7NO_3$	6
2	Benzoxazine	Whole plant		254-18-2	C_8H_7NO	7
3	Benzoxazolinone	Whole plant		59-49-4	$C_7H_5NO_2$	7
4	Coixol	Aerial		532-91-2	$C_8H_7NO_3$	8
5	1-Hydroxy-6-methoxy-2-benzoxazolinon	Aerial		1402088-77-0	$C_8H_7NO_4$	8
6	3,6-Dimethoxy-benzoxazolin-2(3*H*)-one	Aerial		1402088-76-9	$C_9H_9NO_4$	8
7	(2*R*)-2-(β-D-Glucopyranosyloxy)-7-methoxy-2*H*-1,4-benzoxazin-3(4*H*)-one	Aerial		113565-31-4	$C_{15}H_{19}NO_9$	8
8	(2*R*)-2-(β-D-Glucopyranosyloxy)-4,7-dimethoxy-2*H*-1,4-benzoxazin-3(4*H*)-one	Aerial		113565-33-6	$C_{16}H_{21}NO_{10}$	8
9	(2*R*)-7-Methoxy-2*H*-1,4-benzoxazin-3(4*H*)-one 2-*O*-β-galactopyranoside	Aerial		1402088-75-8	$C_{15}H_{19}NO_9$	8
10	7-Methoxy-2,4-hydroxy-1,4-benzoxazin-3(2*H*)-one	Whole plant		15893-52-4	$C_9\ H_9\ NO_5$	3
11	Dextromoramide	Leaves		357-56-2	$C_{25}H_{32}N_2O_2$	9
12	2-Heptadecyl-2-imidazoline	Leaves		105-28-2	$C_{20}H_{40}N_2$	9
13	1-Methyl-2-pyrrolidinone	Leaves		872-50-4	C_5H_9NO	9

Table 1 (*Contd.*)

No.	Compound	Part of plant	Chemical structure	CAS number	Chemical formula	Ref.
14	N^1-Acetylspermine	Leaves		25593-72-0	$C_{12}H_{28}N_4O$	9
15	Cyclohexylamine	Leaves		108-91-8	$C_6H_{13}N$	9
16	Procaine	Leaves		59-46-1	$C_{13}H_{20}N_2O_2$	9
17	Epinephrine	Aerial		51-43-4	$C_9H_{13}NO_3$	11
18	Norepinephrine	Aerial		51-41-2	$C_8H_{11}NO_3$	11

apigenin, luteolin, homoplantaginin, acerosin, pectolinarin, scutellarein, hispidulin, and apigenin-8-*C*-α-L-arabinopyranoside from the 70% aqueous acetone extract of the dry aerial part of *S. dulcis*. Among them, scutellarein, hispidulin, apigenin, and luteolin have been tested to have PPAR-γ (peroxisome proliferator-activated receptor gamma) agonistic effects with EC_{50} values of about 0.9–24.9 μM. Apigenin-7-*O*-glucuronide, hispidulin-7-*O*-glucuronide, nevadensin, cirsimaritin, cirsiliol, and salvigenin were identified by HPLC-MS/MS analysis of methanol extract from leaves of *S. dulcis*.[16] Further experiments showed that the ethyl acetate extracts of *S. dulcis* have potential α-glucosidase and tyrosinase inhibitory activity. Scutellarin, isorhoifolin, and scutellarein 7-*O*-α-glucuronamide were also reported in *S. dulcis*.[7,8,10] The chemical structures of flavones compounds are shown in Table 2.

Flavonols

Flavonols are the second most abundant flavonoids in *S. dulcis*. Three flavonols, morin, dihydroxy-dimethoxyflavone, and hydroxy-tetramethoxyflavone, were identified by HPLC-MS/MS analysis of methanol extract from leaves of *S. dulcis*.[16] Dillenetin 3-*O*-(6″-*O*-*p*-coumaroyl)-β-D-glucopyranoside was isolated from the 70% aqueous acetone extract of the dry aerial part of *S. dulcis*. Experiments showed that this compound had low agonistic activity on PPAR-γ. The 70% ethanol extract of *S. dulcis* showed the presence of rutin, quercetin, and kaempferol. It has been found that kaempferol can alleviate hyperglycemia by inhibiting liver gluconeogenesis, improving liver sensitivity to insulin, and inhibiting inflammatory response and oxidative stress.[17,18] Rutin and quercetin are also known to have antihyperglycemic effects. The glucose lowering mechanisms may include reducing the absorption of carbohydrates in the small intestine, inhibiting tissue gluconeogenesis, increasing tissue uptake and utilization of glucose, stimulating beta cells to secrete insulin, and protecting Langerhans islets from degeneration.[19,20] The chemical structures of flavonols compounds are shown in Table 3.

Other flavonoids

Catechin and naringin were present in the 70% aqueous ethanol extract from aerial parts of *S. dulcis*. They belong to flavan-3-ols and isoflavones respectively. Both catechin and naringin have antihyperglycemic and antihyperlipidemic effects. They are both antioxidants, and naringin seems to alleviate metabolic syndrome by preventing oxidative damage and pro-inflammatory cytokine release.[21,22] The chemical structures of other flavonoids compounds are shown in Table 4.

Diterpenoids

Diterpenoids refer to a group of compounds whose molecular skeleton consists of 4 isoprene units and contains 20 carbon atoms. Giang *et al.*[23] isolated scopadulcic acid A, scopadulcic acid B, scopadulciol, 4-*epi*-scopadulcic acid B, *iso*-dulcinol, scopadulcic acid C, and dulcidiol from the aerial parts of *S. dulcis*. In MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) cytotoxic assay, 4-*epi*-scopadulcic acid B, *iso*-dulcinol, and scopadulcic acid C exhibited cytotoxic activity against KB cells with IC_{50} values ranging from 2–50 μg mL^{-1}. Scopadulcic acid B and scopadulciol were also reported to exhibit gastric proton pump inhibitory activity, specifically scopadulcic acid B was a reversible inhibitor.[24] Dulcinodal, dulcinodiol, and scopadiol decanoate were isolated from petroleum ether extract of aerial parts of *S. dulcis*. They can be classified as labdane-derived diterpenes. 4-*epi*-7α-*O*-Acetylscoparic acid A, 7α-hydroxyscopadiol, (7S)-4-*epi*-7-hydroxyscoparic acid A, 7α-*O*-acetyl-8,17β-epoxyscoparic acid A, *neo*-dulcinol, dulcinodal-13-one, and 4-*epi*-7α-hydroxydulcinodal-13-one were determined by Liu *et al.*[15] from the 70% aqueous acetone extract of the dry aerial part of *S. dulcis* by analysing their NOESY

Table 2 The chemical structures of flavones compounds, extracted from various part of *S. dulcis*

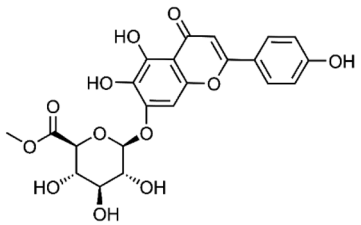
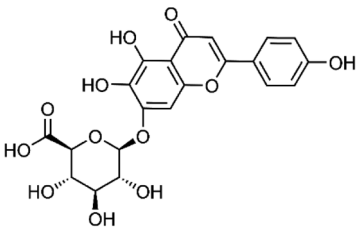
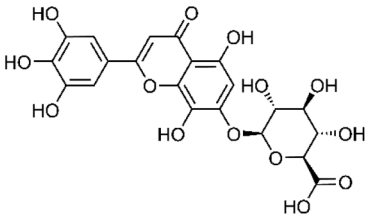
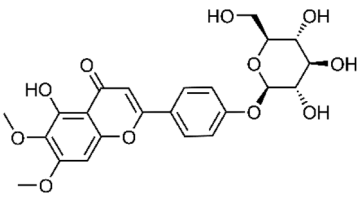
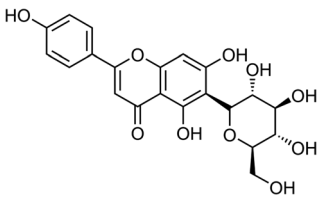
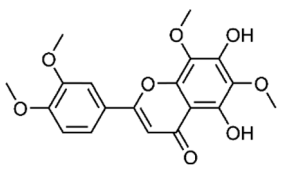
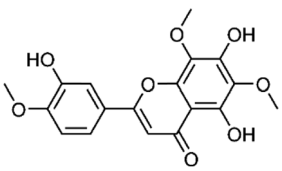
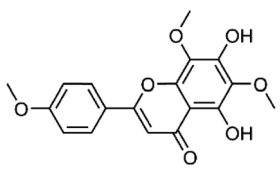
No.	Compound	Part of plant	Chemical structure	CAS number	Chemical formula	Ref.
19	Scutellarin methylester	Whole plant			$C_{22}H_{20}O_{12}$	12
20	Scutellarin	Whole plant		27740-01-8	$C_{21}H_{18}O_{12}$	7
21	5,7,8,3′,4′,5′-Hexahydroxy-flavone glucuronide	Whole plant			$C_{21}H_{18}O_{14}$	12
22	5-Hydroxy-6,7-dimethoxyflavone-4′-*O*-β-glucose	Whole plant			$C_{23}H_{24}O_{11}$	12
23	*iso*-Vitexin	Leaves		38953-85-4	$C_{21}H_{20}O_{10}$	3
24	5,7-Dihydroxy-3′4′,6,8-tetrametoxyflavone	Whole plant		56003-01-1	$C_{19}H_{18}O_8$	13
25	Acerosin	Aerial		15835-74-2	$C_{18}H_{16}O_8$	15
26	Nevadensin	Leaves		10176-66-6	$C_{18}H_{16}O_7$	16

Table 2 (*Contd.*)

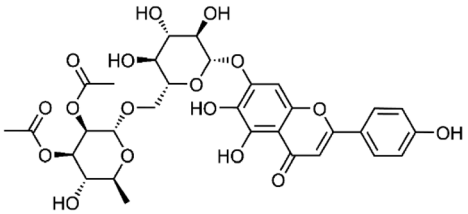
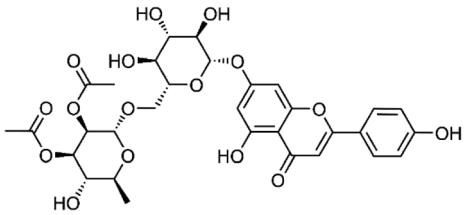
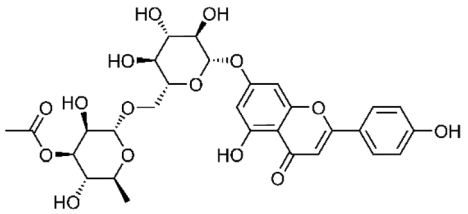
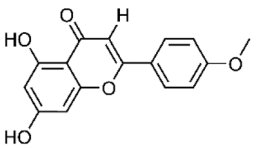
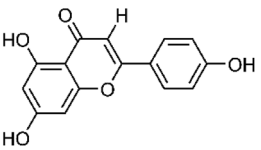
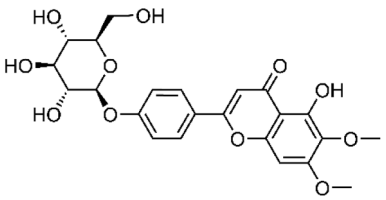
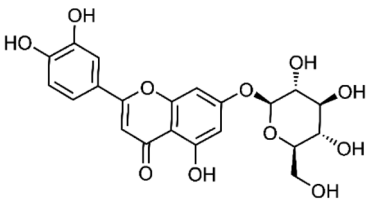
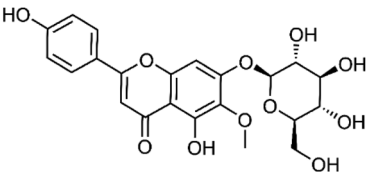
No.	Compound	Part of plant	Chemical structure	CAS number	Chemical formula	Ref.
27	5,6,4′-Trihydroxyflavone 7-*O*-α-L-2,3-di-*O*-acetylrhamnopyranosyl-(1→6)-β-D-glucopyranoside	Whole plant		682354-22-9	$C_{31}H_{34}O_{17}$	14
28	Apigenin 7-*O*-α-L-2,3-di-*O*-acetylrhamnopyranosyl-(1→6)-β-D-glucopyranoside	Whole plant		682354-24-1	$C_{31}H_{34}O_{16}$	14
29	Apigenin 7-*O*-α-L-3-*O*-acetylrhamnopyranosyl-(1→6)-β-D-glucopyranoside	Whole plant		682354-23-0	$C_{29}H_{32}O_{15}$	14
30	Acacetin	Whole plant		480-44-4	$C_{16}H_{12}O_5$	3
31	Apigenin	Whole plant		520-36-5	$C_{15}H_{10}O_5$	15
32	Cirsimarin	Whole plant		13020-19-4	$C_{23}H_{24}O_{11}$	3
33	Cynaroside	Whole plant		5373-11-5	$C_{21}H_{20}O_{11}$	3
34	Homoplantaginin	Aerial		17680-84-1	$C_{22}H_{22}O_{11}$	15

Table 2 (*Contd.*)

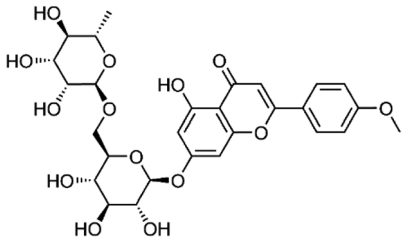
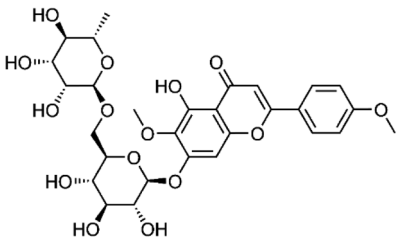
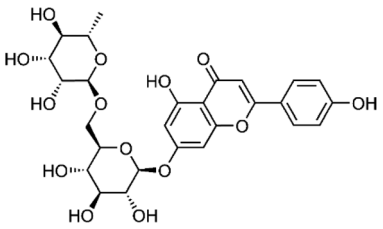
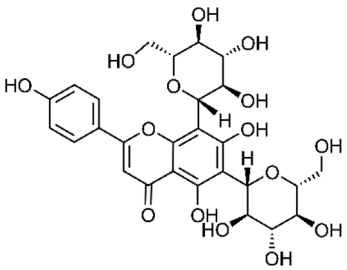
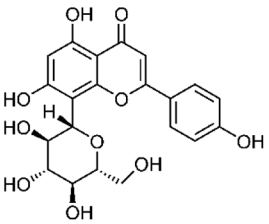
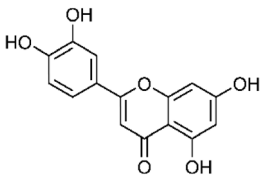
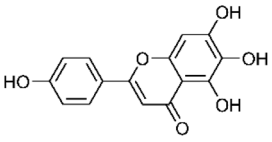
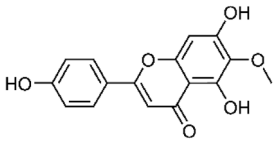
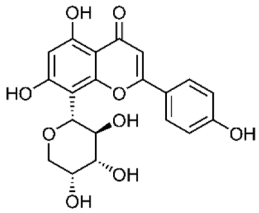
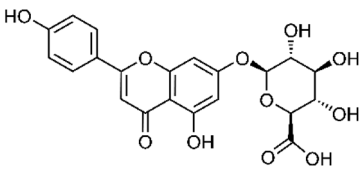
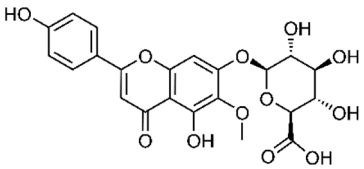
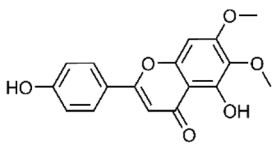
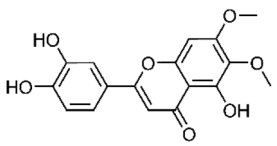
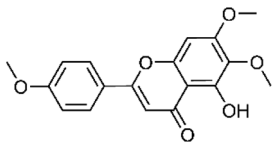
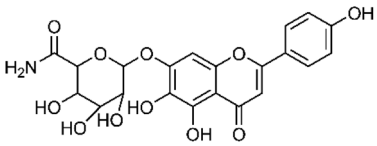
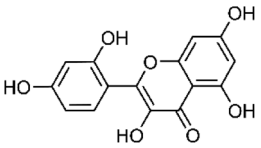
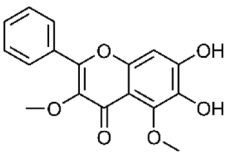
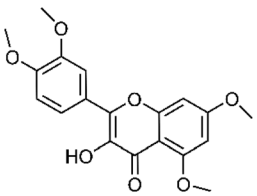
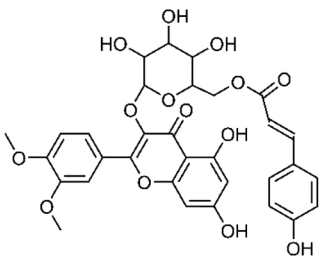
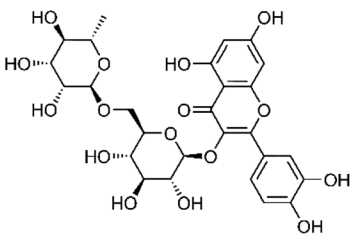
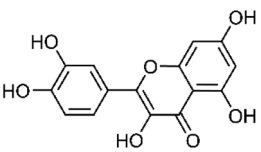
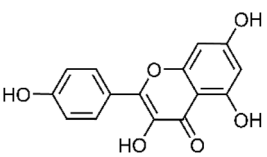
No.	Compound	Part of plant	Chemical structure	CAS number	Chemical formula	Ref.
35	Linarin	Whole plant		480-36-4	$C_{28}H_{32}O_{14}$	3
36	Pectolinarin	Aerial		28978-02-1	$C_{29}H_{34}O_{15}$	15
37	Isorhoifolin	Aerial		552-57-8	$C_{27}H_{30}O_{14}$	7
38	Vicenin-2	Whole plant		23666-13-9	$C_{27}H_{30}O_{15}$	3
39	Vitexin	Leaves		3681-93-4	$C_{21}H_{20}O_{10}$	3
40	Luteolin	Whole plant		491-70-3	$C_{15}H_{10}O_6$	15
41	Scutellarein	Whole plant		529-53-3	$C_{15}H_{10}O_6$	15

Table 2 (*Contd.*)

No.	Compound	Part of plant	Chemical structure	CAS number	Chemical formula	Ref.
42	Hispidulin	Aerial		1447-88-7	$C_{16}H_{12}O_6$	15
43	Apigenin-8-*C*-α-L-arabinopyranoside	Aerial		38642-55-6	$C_{20}H_{18}O_9$	15
44	Apigenin-7-*O*-glucuronide	Leaves		29741-09-1	$C_{21}H_{18}O_{11}$	16
45	Hispidulin-7-*O*-glucuronide	Leaves		31105-76-7	$C_{22}H_{20}O_{12}$	16
46	Cirsimaritin	Leaves		6601-62-3	$C_{17}H_{14}O_6$	16
47	Cirsiliol	Leaves		34334-69-5	$C_{17}H_{14}O_7$	16
48	Salvigenin	Leaves		19103-54-9	$C_{18}H_{16}O_6$	16
49	Scutellarein 7-*O*-α-glucuronamide	Aerial		1402088-78-1	$C_{21}H_{19}NO_{11}$	8

spectra. The inhibitory effect of 4-*epi*-scopadulcic acid B on α-glucosidase (IC_{50}: 14.6 ± 1.5 μM) is more potent than that of acarbose in the positive control group (IC_{50}: 3760 ± 157.2 μM). Scoparic acid A, scoparic acid B, and scoparic acid C were isolated from the whole plant of *S. dulcis*, and their cytotoxic activity was verified by Hayashi *et al.*[13] Scoparic acid E was isolated from the CH_2Cl_2 extract of the dried whole plant of *S. dulcis* by Zhang *et al.*[25] Sun *et al.*[26] isolated scoparicol A and scoparicol B from the aerial parts of *S. dulcis* and various spectroscopic techniques were used to determine their chemical structures. It is worth mentioning that scoparic acid E, scoparicol A, and scoparicol B were all tested for their ability to attenuate plamitate-induced viability at 25 and 50 μM. The result showed that they could all attenuate palmitate-induced viability in MIN6 cells.[25,26] Scoparic acid D, isolated from *S. dulcis*, was compared with miglitol and voglibose, and found to

Table 3 The chemical structures of flavonols compounds, extracted from various part of *S. dulcis*

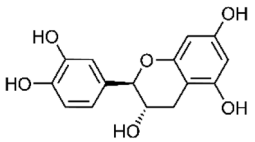
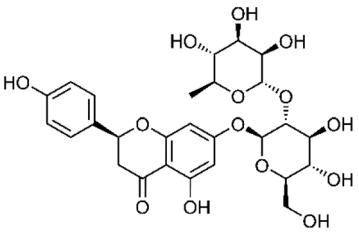
No.	Compound	Part of plant	Chemical structure	CAS number	Chemical formula	Ref.
50	Morin	Leaves		480-16-0	$C_{15}H_{10}O_7$	16
51	Dihydroxy-dimethoxyflavone	Leaves		PubChem CID: 123885531	$C_{17}H_{14}O_6$	16
52	Hydroxy-tetramethoxyflavone	Leaves		1244-78-6	$C_{19}H_{18}O_7$	16
53	Dillenetin 3-*O*-(6″-*O*-*p*-coumaroyl)-β-D-glucopyranoside	Aerial		1613545-05-3	$C_{32}H_{30}O_{14}$	15
54	Rutin	Whole plant		153-18-4	$C_{27}H_{30}O_{16}$	40
55	Quercetin	Leaves		117-39-5	$C_{15}H_{10}O_7$	45
56	Kaempferol	Whole plant		520-18-3	$C_{15}H_{10}O_6$	40

have similar α-glucosidase enzyme inhibitory activity.[27] Hayashi *et al.*[28] isolated scopadulin from the $CHCl_3$-soluble part of *S. dulcis*. It is a tetracyclic diterpene and has antiviral activity. Scopanolal and scopadiol were isolated from the petroleum ether extract of aerial parts of *S. dulcis* by Ahsan *et al.*[29] The two compounds have been confirmed to have anti-gastric cancer activity *in vitro*. In addition, phytol, which is commonly found in plants, also has anti-inflammatory, anti-oxidative, antidiabetic, and antihyperlipidemic effects.[30] The chemical structures of diterpenoids compounds are shown in Table 5.

Triterpenoids

Most triterpenoids are considered to be formed by the condensation of 6 isoprene, so skeleton of most triterpenoids contain 30 carbon atoms. 6 triterpenoids, friedelin, glutinol, α-amyrin, dulcioic acid, betulinic acid, and ifflaionic acid were

Table 4 The chemical structures of other flavonoids compounds, extracted from various part of *S. dulcis*

No.	Compound	Part of plant	Chemical structure	CAS number	Chemical formula	Ref.
57	Catechin	Whole plant		7295-85-4	$C_{15}H_{14}O_6$	40
58	Naringin	Whole plant		10236-47-2	$C_{27}H_{32}O_{14}$	40

identified from petrol extract of *S. dulcis* by Mahato *et al.*[31] Glutinol was confirmed to promote insulin secretion.[32] Betulinic acid has been found to have antidiabetic, anti-inflammatory, antihyperlipidemic, anti-viral, and anti-tumor activities, which provides a pharmacological basis for its use in the treatment of metabolic syndrome.[33] Lupeol and glutenol were reported by Wan *et al.*[34] Glutinone was isolated from the methanol extract of *S. dulcis* by Sharma Khaga *et al.*[32] Glutinone can exert anti-inflammatory activity by inhibiting cyclooxygenase-1 (COX-1).[35] Taraxerol was reported by Babincova *et al.*[7] It exerts anti-inflammatory activity by inhibiting the NF-κB singling pathway.[36] Taraxerol also has antidiabetic activity and was found to attenuate diabetic neuropathy in rats with type 2 diabetes.[37] The chemical structures of triterpenoids compounds are shown in Table 6.

Steroids

So far, there are still relatively few studies on steroids in *S. dulcis*. Steroids may be involved in the metabolism of calcium and phosphorus in the human body. Babincova *et al.*[7] reported three steroids found in *S. dulcis*. They are daucosterol, stigmasterol, and β-sitosterol. It has been reported that stigmasterol has anti-inflammatory and antioxidative effects and can improve the tissue damage caused by the inflammatory response induced by ischemia-reperfusion injury.[38] Daucosterol can also improve cerebral ischemia-reperfusion injury and protect neurons.[25] β-Sitosterol has many pharmacological properties, including anti-inflammatory, antidiabetic, and antihyperlipidemic. Experiments showed that the compound is a promising supplement for the treatment of metabolic syndrome.[39] The chemical structures of steroids compounds are shown in Table 7.

Phenolics

Phenolic compounds widely exist in plants and have aromatic odor. The phenolic compounds sorted out below do not include flavonoids. Datta *et al.*[40] determined chlorogenic acid, caffeic acid, ferulic acid, and sinapic acid from the 70% ethanol extract of *S. dulcis*. Chlorogenic acid can improve blood glucose and lipid levels by regulating gene expression. Additionally, it can lower blood pressure, and has many pharmacological activities, including liver protection, anti-inflammation, and cardiovascular protection.[41] A study showed that the combination of caffeic acid and ferulic acid in the treatment of mice with metabolic syndrome resulted in significant reductions in their blood sugar, cholesterol, and triglycerides levels, and improvement in liver cell steatosis by increasing liver intake of cholesterol and reducing triglyceride synthesis.[42] Sinapic acid has also been confirmed to have antidiabetic, hepatoprotective, anti-inflammatory, anti-oxidative, and cardioprotective effects.[43] Forsythoside G were determined by HPLC-MS/MS analysis of methanol extract from leaves of *S. dulcis*.[16] Acteoside was isolated from the water extract of the dried aerial parts of *S. dulcis* by Wu *et al.*[8] and was confirmed to exert anti-osteoarthritic activity *via* the JAK/STAT signaling pathway.[44] Tin *et al.*[10] investigated the methanol fraction of whole plants of *S. dulcis* and isolated ferruginoside C. *p*-Coumaric acid was reported by Beh *et al.*[45] to have the ability to reverse diabetic nephropathy in their experiments.[46] Gentisic acid reported by Babincova *et al.*[7] also has anti-inflammatory, hepatoprotective, antioxidative, and neuroprotective activities.[47] The chemical structures of phenolic compounds are shown in Table 8.

Other aliphatics

It is reported that mannitol is found in *S. dulcis*.[7] This compound has osmotic diuretic effect, but its oral absorption is low. Hexalure, 2-hexyldecanoic acid, 5*Z*-eicosenoic acid, and methyl arachidate were identified in the aqueous extract of *S. dulcis* by Wankhar *et al.*[9] Wangsa *et al.*[48] also found that stearic acid and methyl stearate in *S. dulcis* have estrogen agonistic effects by using molecular docking technology. The chemical structures of other aliphatics compounds are shown in Table 9.

Table 5 The chemical structures of diterpenoids compounds, extracted from various part of *S. dulcis*

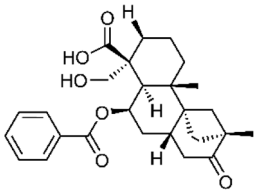
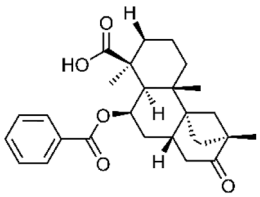
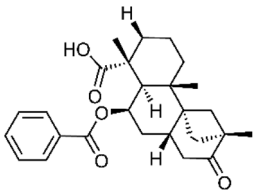
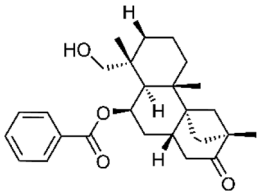
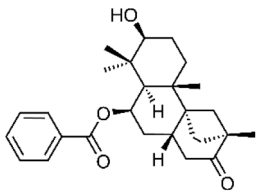
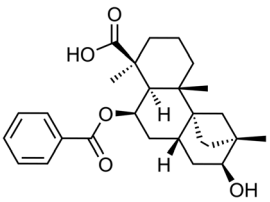
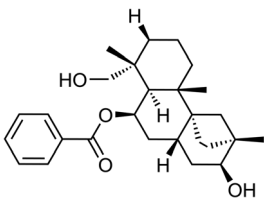
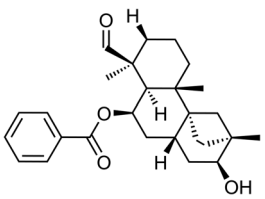
No.	Compound	Part of plant	Chemical structure	CAS number	Chemical formula	Ref.
59	Scopadulcic acid A	Aerial		114804-64-7	$C_{27}H_{34}O_6$	23
60	4-*epi*-Scopadulcic acid B	Aerial		577992-08-6	$C_{27}H_{34}O_5$	23
61	Scopadulcic acid B	Aerial		114804-65-8	$C_{27}H_{34}O_5$	23
62	Scopadulciol	Aerial		136565-26-9	$C_{27}H_{36}O_4$	23
63	*iso*-Dulcinol	Aerial		578714-90-6	$C_{27}H_{36}O_4$	23
64	Scopadulcic acid C	Aerial			$C_{27}H_{34}O_5$	23
65	Dulcidiol	Aerial		578714-91-7	$C_{27}H_{38}O_4$	23
66	Dulcinodal	Aerial		1443044-14-1	$C_{27}H_{36}O_4$	29

Table 5 (*Contd.*)

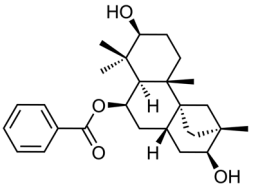
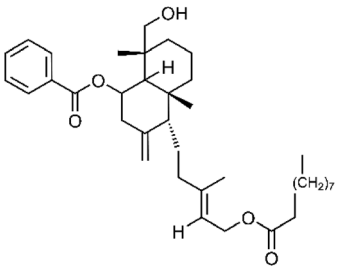
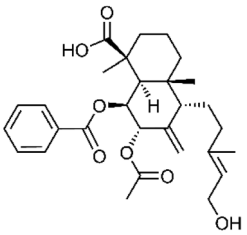
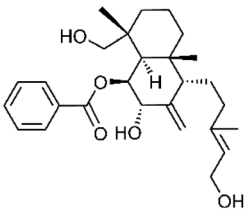
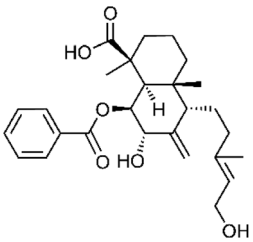
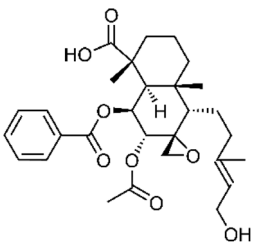
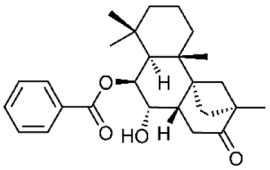
No.	Compound	Part of plant	Chemical structure	CAS number	Chemical formula	Ref.
67	Dulcinodiol	Aerial		1443044-15-2	$C_{27}H_{38}O_4$	29
68	Scopadiol decanoate	Aerial		1443044-16-3	$C_{37}H_{56}O_5$	29
69	4-*epi*-7α-*O*-Acetylscoparic acid A	Aerial		1613544-96-9	$C_{29}H_{38}O_7$	15
70	7α-Hydroxyscopadiol	Aerial		1613544-98-1	$C_{27}H_{38}O_5$	15
71	(7*S*)-4-*epi*-7-Hydroxyscoparic acid A	Aerial		1613545-04-2	$C_{27}H_{36}O_6$	15
72	7α-*O*-Acetyl-8,17β-epoxyscoparic acid A	Aerial		1613545-00-8	$C_{29}H_{38}O_8$	15
73	*neo*-Dulcinol	Aerial		1613692-96-8	$C_{27}H_{36}O_4$	15

Table 5 (*Contd.*)

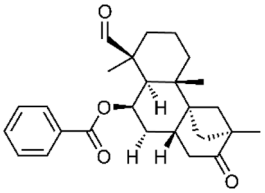
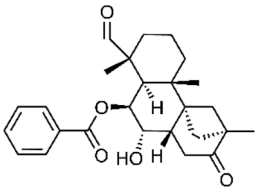
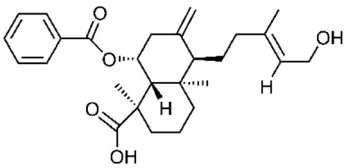
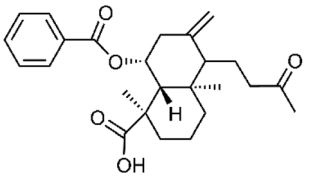
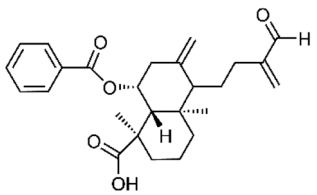
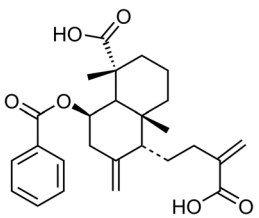
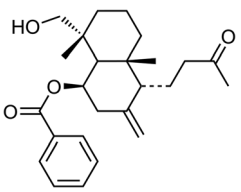
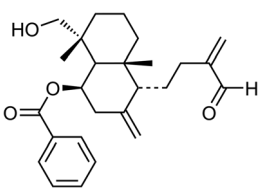
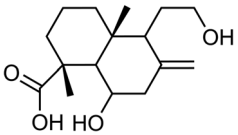
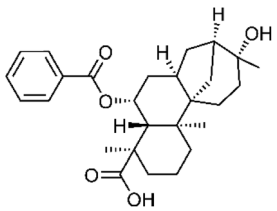
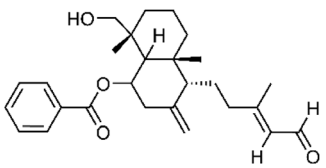
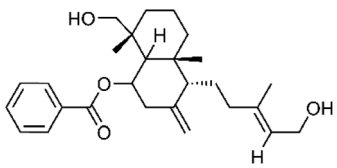
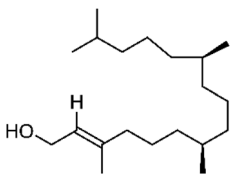
No.	Compound	Part of plant	Chemical structure	CAS number	Chemical formula	Ref.
74	Dulcinodal-13-one	Aerial		1613545-02-0	$C_{27}H_{34}O_4$	15
75	4-*epi*-7α-Hydroxydulcinodal-13-one	Aerial		1613545-03-1	$C_{27}H_{34}O_5$	15
76	Scoparic acid A	Aerial		116425-30-0	$C_{27}H_{36}O_5$	13
77	Scoparic acid B	Aerial		116425-29-7	$C_{25}H_{32}O_5$	13
78	Scoparic acid C	Whole plant		116425-28-6	$C_{26}H_{32}O_5$	13
79	Scoparic acid E	Whole plant			$C_{26}H_{32}O_6$	25
80	Scoparicol A	Aerial			$C_{25}H_{34}O_4$	26
81	Scoparicol B	Aerial			$C_{26}H_{34}O_4$	26

Table 5 (*Contd.*)

No.	Compound	Part of plant	Chemical structure	CAS number	Chemical formula	Ref.
82	Scoparic acid D	Whole plant		1256659-95-6	$C_{16}H_{26}O_4$	27
83	Scopadulin	Whole plant		129058-58-8	$C_{27}H_{36}O_5$	28
84	Scopanolal	Aerial		578714-92-8	$C_{27}H_{36}O_4$	29
85	Scopadiol	Whole plant		130838-00-5	$C_{27}H_{38}O_4$	29
86	Phytol	Leaves		150-86-7	$C_{20}H_{40}O$	49

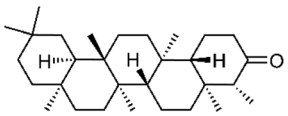
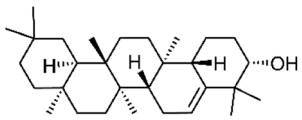
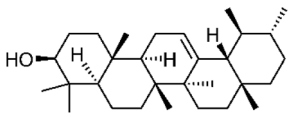
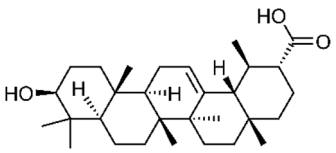
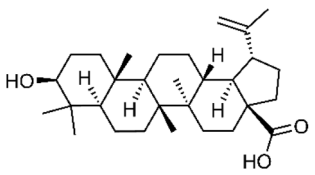
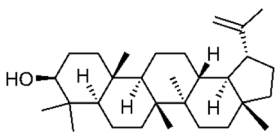
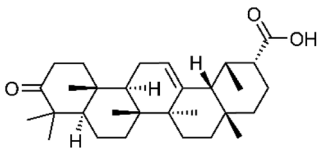
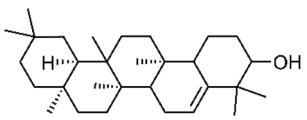
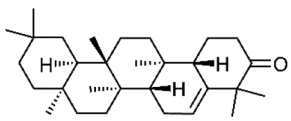
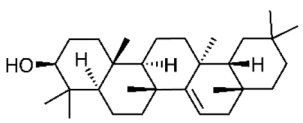
Pharmacological basis to treat metabolic syndrome

In recent years, researchers have studied the chemical components and pharmacological activities of the different extracts from *S. dulcis* and confirmed that *S. dulcis* provides various therapeutic effects related to the treatment of chronic conditions. These include antidiabetic, antihyperlipidemic, anti-atherosclerotic, anti-inflammatory, anti-arthritic, and hepatoprotective properties. This paper aims to investigate the pharmacological effects of *S. dulcis* as they pertain to the treatment of metabolic syndrome and its complications through a review of the existing literature.

Antidiabetic effect

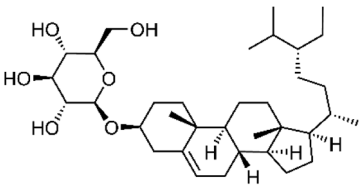
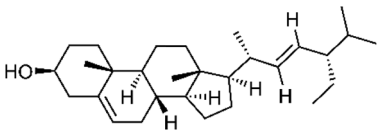
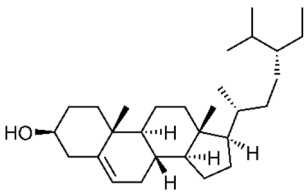
The scoparic acid D (SAD) aqueous extract of *S. dulcis* showed significant antidiabetic activity by decreasing fasting blood glucose levels, increasing the plasma insulin levels and also stimulating insulin secretion from islets to increase plasma insulin levels on streptozotocin (STZ)-induced hyperglycemic rats. An *in vitro* study showed that 20 μg mL^{-1} SAD increased insulin secretion best compared to 16.7 mM glucose (positive control) and 40–80 μg SAD.[50] The insulin-secretagogue activity of the aqueous extract of *S. dulcis* exhibited a significant stimulatory effect on insulin secretion from isolated Balb/c splenic pancreatic islets *in vitro*.[51] The aqueous extract of *S. dulcis* (200 mg kg^{-1}) showed effects on the polyol pathway and lipid peroxidation in the livers of STZ induced diabetic Wistar rats.[52] SAD also exhibited binding affinity to the active site of human α-glucosidase enzyme, comparable to commercial drugs Miglitol and Voglibose.[53] The diabetic rats treated with 200 mg kg^{-1} of the *S. dulcis* plant extract exhibited significant reduction in blood glucose level.[54] Another 15 days experiment also showed a significant anti-hyperglycemic effect of the aqueous *S. dulcis* plant extract.[50,55] When rats with STZ-induced diabetes were administered the *S. dulcis* plant extract, they exhibited a significant blood glucose reduction and an increase in plasma insulin as compared to rats administered with glibenclamide, the standard drug.[56] Additionally, as compared to the standard drug tolbutamide, glutinol from *S. dulcis* caused a moderate insulin secretory activity increase, and coixol from *S. dulcis* showed a significant activity increase.[57,58] The flavonoid extract of *S. dulcis* (400 mg kg^{-1}) was found to decrease the serum glucose level to near normal in a glucose tolerance test and normoglycemic study.[59] Coixol from *S. dulcis* exhibited significant

Table 6 The chemical structures of triterpenoids compounds, extracted from various part of *S. dulcis*

No.	Compound	Part of plant	Chemical structure	CAS number	Chemical formula	Ref.
87	Friedelin	Whole plant		559-74-0	$C_{30}H_{50}O$	31
88	Glutinol	Whole plant		545-24-4	$C_{30}H_{50}O$	31
89	α-Amyrin	Whole plant		638-95-9	$C_{30}H_{50}O$	31
90	Dulcioic acid	Whole plant		78516-69-5	$C_{30}H_{48}O_3$	31
91	Betulinic acid	Roots		472-15-1	$C_{30}H_{48}O_3$	31
92	Lupeol	Whole plant		545-47-1	$C_{30}H_{50}O$	34
93	Ifflaionic acid	Whole plant		6805-19-2	$C_{30}H_{46}O_3$	31
94	Glutenol	Whole plant		137397-38-7	$C_{30}H_{50}O$	34
95	Glutinone	Whole plant		508-09-8	$C_{30}H_{48}O$	32
96	Taraxerol	Whole plant		127-22-0	$C_{30}H_{50}O$	7

antidiabetic activity by improving the glucose tolerance and fasting blood glucose levels in diabetic animals.[57] The α-glucosidase inhibitors with flavonoids such as scutellarein, hispidulin, apigenin, luteolin, and the triterpenoid betulinic acid have been found in *S. dulcis*. 4-*epi*-scopadulcic acid B from *S. dulcis* exhibited significant inhibitory activity against α-glucosidase. Additionally, an *in vitro* study of 4-*epi*-7α-*O*-acetylscoparic acid A, scutellarein, hispidulin, apigenin, luteolin, and

Table 7 The chemical structures of Steroids compounds, extracted from various part of *S. dulcis*

No.	Compound	Part of plant	Chemical structure	CAS number	Chemical formula	Ref.
97	Daucosterol	Whole plant		474-58-8	$C_{35}H_{60}O_6$	7
98	Stigmasterol	Whole plant		83-48-7	$C_{29}H_{48}O$	7
99	β-Sitosterol	Whole plant		83-46-5	$C_{29}H_{50}O$	7

acerosin from *S. dulcis* showed PPAR-γ agonistic activity.[15,60] A flavonoid fraction, containing quercetin, *p*-coumaric acid, luteolin, and apigenin in the ratio of 8 : 26 : 1 : 3, extracted from *S. dulcis* by thin layer chromatography fraction-7 (SDF7), possesses significant glucose uptake activity by upregulating glucose transporter-4 (Glut 4) expression and *trans*-location. Additionally, it showed better glucose transport activity than insulin even in the insulin resistance model induced by free fatty acids. TC 10 was confirmed to promote Glut 4 translocation in immortalized rat skeletal (L6) myotubes by remodelling cellular actin and it can be induced by SDF7.[61] SDF7 was capable of inducing the differentiation of 3T3-F442a adipocytes, stimulating the secretion of adiponectin, and upregulating peroxisome proliferator-activated receptor-γ (PPAR-γ mRNA) on the cells as well as other mechanisms that have already been elucidated.[45] The range of antiglycation potential of *S. dulcis* decoction was 13–213 μg mL^{-1}.[62] Important experiments about the antidiabetic activities of different extracts from *S. dulcis* are listed in Table 10.

Antihyperlipidemic effect

Hyperlipidemia is a well-known complication of diabetes. In diabetic rats treated with 200 mg kg^{-1} of aqueous extract of *S. dulcis*, their serum cholesterol, low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), triglycerides, free fatty acids, and phospholipids were significantly reduced, while their high-density lipoprotein (HDL) levels were elevated. The activity of rat hepatic hydroxymethylglutaryl-CoA (HMG-CoA) reductase was also significantly reversed towards normalization after treating with an aqueous extracts of *S. dulics*.[63] An aqueous extract of *S. dulcis* plant can increase serum high-density lipoprotein cholesterol, anti-atherogenic index, and HMG-CoA reductase activity, resulting in an antihyperlipidemic effect.[63] The methanolic extract of *S. dulcis* can increase uptake of glucose at tissue level and increase pancreatic β-cell function or due to inhibition of intestinal glucose absorption of glucose, producing significant antihyperglycemic activity.[59] Porridge with fresh *S. dulcis* leaf extract decreased fasting blood glucose (FBG) and glycated hemoglobin (HbA1c) of type 2 diabetic patients. This porridge had no effect on cholesterol measurements and no toxicity; therefore, this porridge is a suitable meal for diabetic patients.[64]

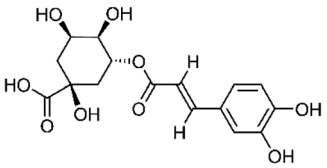
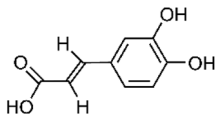
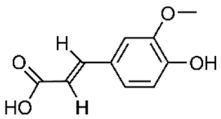
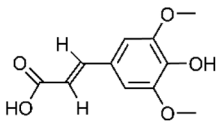
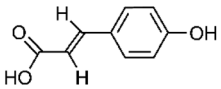
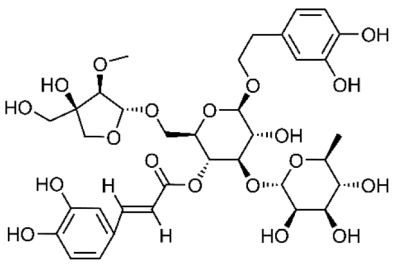
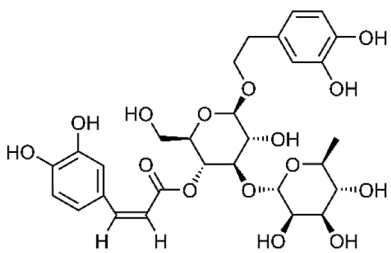
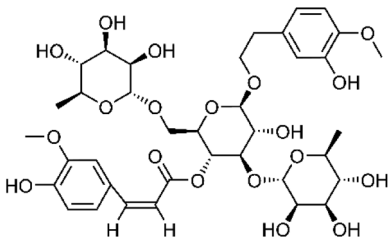
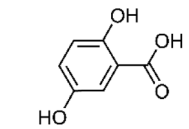
Anti-inflammatory effect

The anti-inflammatory activity of *S. dulcis* was confirmed on rat paw edema induced by carrageenan.[65] Oral treatment with ethanol extract of the *S. dulcis* inhibited the carrageenan-induced edema.[66] The anti-inflammatory property of *S. dulcis* was investigated on the model of carrageenin-induced pleurisy, suggesting that ethanol extract played a crucial role in inhibiting the production of exudate and leucocyte migration. Water extract of *S. dulcis* was endowed with anti-inflammatory potential in rat paw edema induced by carrageenan or dextran.[65,66] The 70% ethanol extract of *S. dulcis* and betulinic acid, one of the triterpenoids extracted from *S. dulcis*, exhibited a significant anti-inflammatory effect by mitigating the development of λ-carrageenan induced edema.[66]

The anti-inflammatory activity of *S. dulcis* of both 70% ethanol extract of *S. dulcis* and betulinic acid not only significantly inhibited the cyclooxygenase-2 (COX-2) activity in the edema tissue, but also decreased the tissue concentration of nitric oxide (NO), tumor necrosis factor alpha (TNF-α), interleukin-1β (1L-1β), and malondialdehyde (MDA).[67]

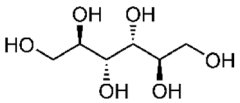
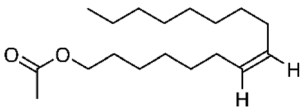
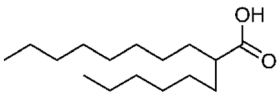
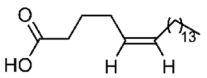
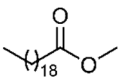
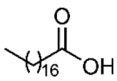
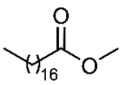
In vitro experiments utilizing the lipopolysaccharide (LPS)-stimulated in RAW 264.7 macrophages,[10] treatment with both ethanol and ethyl acetate extracts of its aerial part showed a significant nitric oxide (NO) production inhibitory potency at 30 and 100 μg mL^{-1}, whilst 100 μg mL^{-1} hexane extract of its

Table 8 The chemical structures of phenolic compounds, extracted from various part of *S. dulcis*

No.	Compound	Part of plant	Chemical structure	CAS number	Chemical formula	Ref.
100	Chlorogenic acid	Whole plant		327-97-9	$C_{16}H_{18}O_9$	40
101	Caffeic acid	Whole plant		331-39-5	$C_9H_8O_4$	40
102	Ferulic acid	Whole plant		1135-24-6	$C_{10}H_{10}O_4$	40
103	Sinapic acid	Whole plant		530-59-6	$C_{11}H_{12}O_5$	40
104	*p*-Coumaric acid	Leaves		7400-08-0	$C_9H_8O_3$	45
105	Forsythoside G	Leaves		129802-19-3	$C_{35}H_{46}O_{19}$	16
106	Acteoside	Aerial		61276-17-3	$C_{29}H_{36}O_{15}$	8
107	Ferruginoside C	Aerial		213991-03-8	$C_{37}H_{50}O_{19}$	10
108	Gentisic acid	Whole plant		490-79-9	$C_7H_6O_4$	7

aerial part was observed to exert the same effect. Glutinone, an isolation from hexane fraction of methanol extract of *S. dulcis*, was observed to exert a moderate effect in inhibition of TNF-α and a weak effect in inhibiting IL-1β and NO production.[32] Ethanol extract of *S. dulcis* also exerted its anti-inflammatory effect on ovalbumin-induced rat paw edema.[68]

Table 9 The chemical structures of other aliphatics compounds, extracted from various part of *S. dulcis*

No.	Compound	Part of plant	Chemical structure	CAS number	Chemical formula	Ref.
109	Mannitol	Whole plant		87-78-5	$C_6H_{14}O_6$	7
110	Hexalure	Leaves		23192-42-9	$C_{18}H_{34}O_2$	9
111	2-Hexyldecanoic acid	Leaves		25354-97-6	$C_{16}H_{32}O_2$	9
112	5*Z*-Eicosenoic acid	Leaves		7050-07-9	$C_{20}H_{38}O_2$	9
113	Methyl arachidate	Leaves		1120-28-1	$C_{21}H_{42}O_2$	9
114	Stearic acid	Whole plant		57-11-4	$C_{18}H_{36}O_2$	48
115	Methyl stearate	Whole plant		112-61-8	$C_{19}H_{38}O_2$	48

As for components isolated from *S. dulcis*, glutinol and glutinone are two potential anti-inflammatory agents involved in the inflammation. It is noteworthy that both glutinol and ethanol extract only exert an active anti-inflammatory effect at the beginning of inflammatory process, approximately 2 hours after administration. This result suggests that glutinol and ethanolic extract of *S. dulcis* may not inhibit the activity of COX. It was observed that extract of *S. dulcis* did not interfere with prostaglandins that induced swelling and vasodilatation.[66] Both indomethacin and ethanol extract barely affected the chronic inflammation models because they were stimulated by other agents which acted in a way different from that of nonsteroidal anti-inflammatory substances.

Anti-atherosclerotic effect

When the hyperglycaemia of diabetic patients makes blood vessels throughout the body fragile and easily injured, so that the walls of blood vessels become inflamed by damage, causing platelets to concentrate on the damaged areas to repair the condition, it will lead to "atherosclerosis" causing cardiovascular diseases. Atherosclerosis affects many organs of the body, leading to strokes, ischemic heart disease, and gangrene in the lower extremities. Dyslipidemia, hypertension, diabetes as well as genetic factors are the main risk factors of atherosclerosis. As for the dyslipidemia, it's clear that LDL accumulates in the endothelium after passing through the arterial wall, in which LDL is likely to convert into oxidized low-density lipoprotein (oxLDL). oxLDL is the key factor leading to atherosclerosis. oxLDL can stimulate inflammation signals and cause macrophages or smooth muscle cells to take up cholesterol to form foam cells. Going a step further, foam cells form fatty streaks that mark the condition of atherosclerosis.[69] Therefore, detecting the antioxidant and anti-inflammatory activities of the extract of *S. dulcis* is helpful for the further study of its anti-atherosclerotic mechanism.

In vivo animal test results showed that an aqueous suspension in clean drinking water of pulverized *S. dulcis* reduced total cholesterol, trriacylglycerol, and LDL-cholesterol and HDL-cholesterol was also significantly reduced.[70] The foliar methanol extract of *S. dulcis* inhibited LDL and its oxidation to oxLDL to prevent foam cell formation, provided with strong anti-atherogenic potential.[71,72]

Hepatoprotective effect

Metabolic diseases are prone to the non-alcoholic fatty liver disease (NAFLD). *S. dulcis* has been used to treat this disease.[34,73] Therefore, some research achievements verified this herbal hepatoprotective activity by using various extracted ingredients of the herb, such as whole plants, roots,and foliar, using a variety of organic solvents. The ethanol extract of *S. dulcis* increased serum alanine aminotransferase (ALT) and aspartate amino-transferase (AST) and elevated the content of reduced glutathione (GSH), while decreasing the malondialdehyde (MDA) level. The hepatoprotective effect was achieved by preventing descending the antioxidative enzymes of superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione

Table 10 The important experiments of antidiabetic activities of different extract/isolate from different parts of *S. dulcis*[a]

Extract/isolate	Plant parts	*In vitro*/*in vivo*	Method	Effects	Control used	Ref.
H_2O	Whole plant	*In vivo*	Blood glucose and plasma insulin determination	The 200 mg kg^{-1} b.w. extract exhibited significant activity in decreasing the fasting blood glucose level to 98 ± 3 mg dL^{-1} compared to the glibenclamide of 114 ± 9 mg dL^{-1}. The plasma insulin level was increased to about 11 μU mL^{-1} when treated with the extract as compared to glibenclamide of 9 μU mL^{-1}	600 μg kg^{-1} glibenclamide (PC), STZ induced diabetic rats (NC), and normal group	92
EtOH	Whole plant	*In vivo*	Streptozotocin induced diabetic rats	Scoparic acid D administered to STZ-induced hyperglycemic rats showed significant plasma insulin increasing activity at the dose of 20 mg kg^{-1} SAD	Compared with the normal group	93
MeOH	Whole plant	*In vitro*	Islet isolation, MIN-6 cell culture and insulin secretion assay	Coixol showed a significant insulin secretory activity (230.35 ± 11.12%) at the dosage of 200 μM, which was more than tolbutamide (212.01 ± 16.76%)	16.7 mM glucose, tolbutamide (PC)	58
H_2O	Whole plant	*In vivo*	Streptozotocin induced diabetic rats	Exhibited significant antihyperglycemic effect ($p < 0.01$). At first glucose was administered orally and then SPEt was treated. After 120 min, the blood glucose level of rats was close to normal (98.8 ± 5.7 mg dL^{-1}) with a dosage of 200 mg kg^{-1} SPEt	Diabetic control (NC) and normal group	51
H_2O	Whole plant	*In vitro*	Islet isolation and incubation	Islets incubated with 10 μg mL^{-1} of SPEt increased insulin secretion to 7 μIU mL^{-1} compared with about 4 μIU mL^{-1} of PC and 1 μIU mL^{-1} of NC	16.7 mM glucose (PC), and 5 mM STZ (NC)	51 and 54
H_2O	Whole plant	*In vivo*	Oral glucose tolerance test	All groups were treated with 2 g kg^{-1} mL^{-1} glucose in advance. Normal groups treated with SPEt showed almost the same blood glucose level compared to untreated groups after 120 min. Diabetic groups treated with 200 mg kg^{-1} SPEt showed significant antihyperglycemic effect (98.96 ± 5.70 mg dL^{-1}) compared to the control groups (326.91 ± 4.40 mg dL^{-1}) and 600 μg kg^{-1} glibenclamide (117.70 ± 6.76 mg dL^{-1})	Glibenclamide (PC), normal and diabetic control groups	55

[a] PC, positive control; NC, negative control; b.w., body weight; SPEt, *S. dulcis* plant water extract.

reductase (GRd), and glutathione-*S*-transferase (GST) to decrease the damage of lipid peroxidation.[74] The hepatoprotective effect of herbal extracts, decreasing the increased ALT, AST, bilirubin, and cholesterol, was compared with that of suitable silymarin to verify its hepatoprotective effect.[75,76] The other *in vivo* test also displayed that the herbal extracts decrease the levels of ALT and AST and increase the level of albumin in carbon tetrachloride (CCl_4)-induced liver injury in mice. Less vacuole form, neutrophil infiltration, and hepatocyte necrosis were also present in histopathological analysis in CCl_4-induced liver injury in mice.[77] Histological and serum biochemistry analysis are necessary as parameters to reflect the improvement of liver function status, containing GSH, MDA and so on.[77] Data comparison confirms the antihepatotoxic activity and hepatocurative activity of *S. dulcis* extract.

Anti-oxidative effect

Oxidative stress is the core pathogenesis of diabetes complications, due to excessive oxygen ions. There are four substances for the removal of free radicals, including SOD, methionine sulfoxide reductase (MSR), catalase (CAT), and GPx.

The aqueous extract of *S. dulcis* showed significant activity in reducing the plasma lipid peroxidation. The parameters of 2-thiobarbituric acid reacting substances test and thiobarbituric acid reactive substances (TBARS) assay, hydroperoxides, and ceruloplasmin were reduced and the activities of plasma insulin, superoxide dismutase, catalase, glutathione peroxidase, glutathione-*S*-transferase, and reduced glutathione were increased.[50] These extracts can significantly reduce the degree of lipid peroxidation in STZ induced diabetic rats and also found that the values and effects of CAT, SOD, GPx, and GSH were slightly better than those of gelibenclamide.[50] Otherwise, these extracts significantly reduced the lipid peroxidation and intracellular reactive oxygen species (ROS) level.[51] The activities of both CAT and MDA were increased by cadmium while the SOD activity was attenuated in the *in vivo* test of rats' liver, kidney, and heart. Coadministration of aqueous extract of *S. dulcis* at dose of 1000 mg kg^{-1} and $CdCl_2$ showed restored activities of both SOD and CAT.[78]

The presence of phenol, flavonoids, and total antioxidants in the methanol and aqueous extract of *S. duicis* displayed that the methanol extract method has effective extraction solvents, which provided higher reduction content than that of aqueous solvents.[9]

The antioxidant activity of 70% ethanol extract of *S. dulcis* was also assessed in the *in vivo* antioxidant enzymes assay and found that the levels of antioxidant enzyme (SOD, GPx, and GRd) activities were significantly increased.[67] The aqueous leaf extract of *S. dulcis* for treatment of brain in the noise environment showed that the levels of H_2O_2, NO, and lipid peroxide in the brain of rats induced by noise could be significantly reduced and protein thiols could be increased. Immunohistochemical study of brain tissue showed that these extracts could down-regulate the expression of neuronal nitric oxide synthases (nNOS) and calcium-insensitive NOS (iNOS) in rat brain. The levels of SOD, CAT, GPX, and GST in the brain of rats treated with the extract were significantly decreased, while the levels of GR, GSH, vitamin C, and vitamin E were significantly increased. In addition, histopathological study showed that the extract of *S. dulcis* could reduce the changes of cerebral cortex caused by noise.[79]

Besides, the aqueous extract of *S. duicis* had the excellent antioxidant and dose-dependent antioxidant index. Both methanol and aqueous extract were provided with the potential free radical scavenging activity at 2,2-diphenyl-1-pyridyl hydrazine (DPPH) model.[80] The anti-oxidant activity of various extract method were compared by their inhibition of xanthine oxidase and lipoxygenase. The hexane, methanol and chloroform extracts of the whole plant produced weak to moderate activity in inhibition of xanthine oxidase and exhibited significant inhibitory activity in lipoxygenase inhibition. All extracts (hexane, chloroform, and methanol) of *S. dulcis* exhibited more than 50% inhibition on lipid peroxidation. Additionally, the results indicated that methanol extract of *S. dulcis* performed better in the inhibition of lipid peroxidation, compared with ascorbic acid extract.[81] The hydroalcoholic extract of *S. dulcis* also exhibited significant antioxidant activity in NO radical and DPPH free radical scavenging activity test.[82] The methanol extract of *S. dulcis* can significantly reduce H_2O_2-induced oxidative stress in Sf9 cells.[83] There are some important experiments about the anti-oxidant and antiatherogenic activities of different extract/isolate from different parts of *S. dulcis*, listed in Table 11.

Hyper/hypotensive effect

The aqueous fraction of ethanol extracts of *S. dulcis* can contract the muscle of vas deferens of rats similar to norepinephrine dose dependently. The left atria incubated with the aqueous fraction of the *S. dulcis* extract showed enhanced contractile force. Histamine induced tension of tracheal rings could be inhibited by aqueous fraction of the extract and epinephrine.[66] The polar extract of the aerial parts of *S. dulcis*, containing noradrenaline and adrenaline substances, displayed the hypertensive effect *in vivo*, relaxing the tracheal smooth musculature and increasing inotropism in heart muscle.[11] Nevertheless, the experimental results of Esume *et al.* 2011[88] showed that higher dose of the water and methanol extracts of *S. dulcis* significantly increased blood pressure from baseline values of animal tests. Although *S. dulcis* plant has been widely used in the treatment of hypertension, the effect of treating hypertension needs more scientific research to demonstrate its therapeutic effect.

Clinical studies

Clinical study is the third stage of drugs development at the aim of providing basis for administration methods, evaluating the safety, measuring the efficacy, and further test. A randomized crossover clinical trial was carried out by Subhashinie *et al.*[64] to show the antihyperglycemic effects of herbal porridge with *S. dulcis* leaves extract in diabetics in Sri Lanka by confirming the antihyperglycemic effects of herbal porridge made of *S. dulcis*

Table 11 The important anti-oxidant and anti-atherogenic activities of different extract/isolate from different parts of *S. dulcis*[a]

Extract/isolate	Plant parts	*In vitro*/*in vivo*	Method	Effects	Control used	Ref.
EtOH	Whole plant	*In vitro*	TBARS analysis	The increased MDA was restored to normal level by 200 mg kg^{-1} silymarin and 0.5 g kg^{-1} EtOH extract. Besides, the extract at the dose of 1.0 mg kg^{-1} could continuously decrease the level of MDA	Silymarin (PC), control group, and CCl_4 group (NC)	74
70% aqueous ethanol and MeOH	Whole plant	*In vitro*	Thiocyanate method and spectrophotometry	The percentage of preventing lipid peroxidation was 42.006 ± 0.797% using 70% aqueous ethanol as extractant and 23.836 ± 0.273% using methanol as extractant	Groups without the extract (NC)	40
MeOH	Aerial	*In vitro*	MTT survival assay	The extract increased viability of Sf9 cells exposed to 750 μM and 1 mM H_2O_2	750 μM and 1 mM H_2O_2 (NC) and normal group	83
70% EtOH/ betulinic acid	Whole plant	*In vivo*	SOD, GPx, and GRd assay	Ethanolic extracts (0.5 and 1 g kg^{-1}), betulinic acid (40 mg kg^{-1}) and indomethacin (20 mg kg^{-1}) significantly increased the levels of SOD, GPx, and GRd activities	Indomethacin (PC)	67
Hexane, CCl_3, and MeOH	Whole plant	*In vitro*	Liver lipid peroxidation assay	All extracts showed significant inhibition effect on lipid peroxidation. Methanol extract showed the highest percentage of inhibition on lipid peroxidation among tested extracts and positive control	Ascorbic acid (PC)	81
MeOH	Leaves	*In vitro*	Spectrophotometry	The methanol extract had the most efficient lipid peroxidation inhibition activity. Besides, the IC_{50} value of methanol extract was slightly higher than the BHA	BHA (PC)	71
MeOH, EtOAc, acetone, and hexane	Leaves	*In vitro*	Oil red O stain	There was evident reduction of oxLDL-treated cells or no foam cells after adding 30 μg mL^{-1} methanol extract	Cells treated with oxidized LDL (NC)	71

[a] PC, positive control; NC, negative control; BHA, butyl hydroxyl anisole.

leaves extract in diabetics in Sri Lank. The total porridge used for treatment is 40 g, and the porridge contains about 13–15 g of fresh *S. dulcis* leaves. As a result, this porridge has the characteristic of decreasing the Fasting Blood Glucose and HbA1c with no effect on cholesterol measurements. At the dose test, no toxicity was observed. Consequently, the porridge made with *S. dulcis* leaves extract can be widely used in commercial products and sold to type 2 diabetic patients.

35 mild to moderate type 2 diabetes patients complete more than six months of trial. Their age ranged between 35–70 years old. The fasting blood glucose is between 127 mg dL^{-1} and 302 mg dL^{-1}. The extruded meals and porridge were prepared with tender leaves extract of *S. dulcis.* 35 participations are divided into two groups taking different meals at the same stage. The clinical trial period consists of three phases. At the first stage, group 1 as the test group eat specific porridge once a day, 3 days per week, for three months; group 2 as the control group eat normal breakfast without *S. dulcis* leaves extract maintaining the same time period and the same frequency. The second period is a wash-out period to prepare for the next crossover trial, lasting for a week. At the last period, group 1 as the control group eat normal breakfast once a day, 3 days per week, for three months; group 2 as the test group eat this porridge.

At the beginning and end of the first and third stages, experimenter measure the following data of 35 participants: glucose measurements (including fasting blood glucose and HbA1c), lipid measurements (including total cholesterol, HDL-C, LDL-C, triglycerides, and cholesterol ratios), and the toxicity paraments (including liver enzymes, creatinine, CRP, and eGFR). Fasting blood glucose at the test trial are all lower than the measurement results at the control trial. Comparing the test results before and after first and third stages, HbA1c shows a downward trend in the test group instead of upward trend in the control group. Lipid measurements showed slight but irregular changes between test and control group. The result of toxicity parameters is normal with no significant difference within or between two groups in first and third stages.

In summary, herbal porridge made of *S. dulcis* leaves extract has antihyperglycemic effect with little to no effect on the cholesterol and toxicity measurements. This randomized crossover clinical trial reveals the feasibility of commercial production of this porridge for type 2 diabetic patients.

Toxicological studies

The toxicity of coixol was evaluated in the *in vitro* MTT assay and showed nontoxic in both MIN-6 and 3T3 cell lines (IC_{50} > 200 μM). Acute and subacute toxicity evaluated in mice showed no significant changes in serum creatine, ALT, and AST, no other abnormal manifestation and no death at 100 mg kg^{-1} body weight, suggesting that coixol was nontoxic in kidney and liver.[32] Coixol administered intravenously showed no toxic effects.[64] Mice treated with 20, 100, and 500 mg kg^{-1} of coixol also exhibited no toxic manifestations.[32] Ethanolic extract of whole plants of *S. dulcis* (EESD) exhibited no toxic effect after the observation period of 72 h when administered orally at doses of 1000, 2000, and 3000 mg kg^{-1}.[84] The aqueous extract of *S. dulcis* at a dosage of 8 g kg^{-1} administered orally exhibited no mortality, no changes in posture, motor activity, and behavior in rats compared to the control group. The 30 days' administration of the extract did not show any gross poisoning symptoms or deaths, but histopathological examination showed mild portal, vascular, stroma, and interstitial congestion in liver, heart, testis, and lung respectively.[85]

An acute toxicity study showed that administration of both aqueous and methanol extract of *S. dulcis* at doses up to 5 g kg^{-1} in rats produce no mortality,[86] morphological, and behavioral toxic effects. A 28 days sub-chronic toxicity study using aqueous and methanol extracts of *S. dulcis* administration in rats (500, 1000, and 1500 mg kg^{-1}) exhibited no obvious difference (p > 0.05) in hematological parameters such as red blood cells (RBC), hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean cell hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and platelets (PLT) when compared with the control group treated with distilled water (1 mL kg^{-1}) only. At the same time, the liver toxicity test of aqueous and methanol leaf extracts were also carried out and some biochemical parameters were measured. The methanol extract (500, 1000, and 1500 mg kg^{-1}) treated rats showed no significant difference (p > 0.05) of ALT and AST level compared to the normal groups. The aqueous extract at doses of 500 and 1000 mg kg^{-1} treated rats exhibited a slight increase in AST. However, the 1500 mg kg^{-1} aqueous extract treated rats showed no significant difference of ALT and AST level. The aqueous and methanol extract of *S. dulcis* at doses of 500, 1000, and 1500 mg kg^{-1} exhibited no significant difference (p > 0.05) in parameters of total protein (TP), alkaline phosphatase (ALP), and serum albumin (ALB). The kidney toxicity of *S. dulcis* was also tested by measuring the parameters of urea and creatinine in urine. Data showed that the aqueous extract of *S. dulcis* administered orally at doses of 500, 1000, and 1500 showed no significant difference of urea and creatinine level compared to the control group. But when treated with 1000 mg kg^{-1} of methanol extract, the urea level significantly increased to 118.98 ± 8.20 μmol L^{-1} compared to the normal group of 53.45 ± 13.93 μmol L^{-1}. The methanol treated groups at other doses exhibited no significant difference compared to the control group. Some tissue injuries were observed in histopathological studies. The kidney section of rats treated with 500 mg kg^{-1} of aqueous and methanol leaf extracts showed slight lymphocyte hyperplasia and tubular necrosis; the 1000 mg kg^{-1} treated groups showed moderate lymphocyte hyperplasia and mild tubular adhesion; 1500 mg kg^{-1} treated groups showed mild lymphocyte hyperplasia. The liver section of rats treated with 500 mg kg^{-1} of aqueous leaf extracts showed mild necrosis and cytoplasmic vacuolation; 1000 mg kg^{-1} treated groups showed moderate Kupfer cell hyperplasia and hepatocellular necrosis; 1500 mg kg^{-1} treated groups exhibited normal features, but showed mild hepatocellular necrosis in the methanol extract treated groups.[87]

The rats treated with 0.01–2 g kg^{-1} ethanolic-aqueous extracts orally exhibited no behavioral change and toxicological signs. When the extract at doses higher than 0.1 g kg^{-1} administered to rats intraperitoneally, significant piloerection

and spontaneous motor activity were observed. After that, the animals died six hours later.[11] Rats injected intraperitoneally with 100 mg kg^{-1} and 200 mg kg^{-1} of water and methanol extract did not die. The LD_{50} values of aqueous and methanol extract of *S. dulcis* administered intraperitoneally using arithmetic method of karber were measured, which were 535 mg kg^{-1} and 390 mg kg^{-1} respectively, indicating the methanol extract was more toxic.[88]

Discussion and conclusion

A considerable number of chemical constituents were isolated and identified from *S. dulcis* and evaluated by their different pharmacological activities. However, there is ample scope to explore many more bioactive compounds based on this plant's varied geographical locations. Further studying their biological properties and mechanism of action will greatly benefit the development of new therapeutic agents.

Research has shown that α-glucosidase inhibitors (AGIs), extracted from *S. dulcis*, demonstrated definitive benefits on glycemic control and postload insulin levels for patients with type 2 diabetes.[89] Flavonoids, terpenoids, and fatty acids extracted from *S. dulcis* can increase insulin sensitivity in patients with diabetes. Peroxisome proliferator-activated receptors (PPARs) agonists found in *S. dulcis* also have reproducible renoprotective effects on diabetic kidney disease through PPAR-independent pathways.[90] Furthermore, the aqueous extract of *S. dulcis* (SAD) showed significant antidiabetic activity in decreasing fasting blood glucose level, increasing the plasma insulin level, and stimulating insulin secretion. SAD also exhibited fine affinity to the active site of human α-glucosidase enzyme, comparable to commercial drugs Miglitol and Voglibose. Glutinol from *S. dulcis* showed moderate insulin secretory activity while coixol showed significant activity as compared to the standard drug tolbutamide. The flavonoid extract of *S. dulcis* decreased the serum glucose level to near normal in glucose tolerance test and normoglycemic study, demonstrating antihyperglycemic activity. Coixol from *S. dulcis* exhibited significant antidiabetic activity in improving the glucose tolerance and fasting blood glucose levels in diabetic animals. A flavonoid fraction extracted from *S. dulcis* showed higher glucose transport activity than insulin even in the insulin resistance model induced by free fatty acids. However, this study does not discuss the potential toxicity of ultra-high doses of *S. dulcis* extracts which may cause liver or kidney damage. More toxicological studies on humans should also be further carried out in the future.

Review of Freire *et al.* in 1993, Chow *et al.* in 1974 and Esume *et al.* 2011 found that dose dependent hypertension produced by the ethanolic extract of *S. dulcis* and its aqueous fraction is useful for treatment of hypertension.[66,88,91] However, low-dose norepinephrine and epinephrine are easily degraded in the digestive tract after oral administration and are not absorbed into the blood in significant amounts. Nevertheless, the test results of Esume *et al.* 2011 [88] also display that the higher doses of the aqueous and methanol extract of *S. dulcis* leaves significantly increased blood pressure, heart rate and mean arterial pressure. Therefore, therapeutic effect of *S. dulcis* on blood pressure needs to be tested clinically to substantiate claims of producing medicinal value.

The aspect of this review can assist the future study to clarify the compatibility of compound prescription in the treatment of metabolic diseases based on the ethnomedicines. 115 active chemical compounds in *S. dulcis* and their pharmacological activities have been elucidated in phytochemical studies. Particularly, scoparic acid is a unique compound of *S. dulcis* that may have extensive pharmacological activity and is the material basis for its treatment of metabolic syndrome. Therefore, the research of the pharmacological interactions of *S. dulcis* with the other medicinal herbs should be further conducted, which not only promotes the therapeutic activity for metabolic diseases but also develops new medicine for treating chronic conditions. For example, parts of pharmaceutical utility of *S. dulcis* with other medicinal herbs have not been deeply investigated, such as the treatment for kidney stones, diuresis, cardiovascular protection, and anticancer effects.

At present, only a fraction of chemical profile has been identified for *S. dulcis.* Further research may isolate additional chemical substances through other extraction methods on various part of this plant. It may be more meaningful from the perspective of new medicine development to guide the separation and extraction of new compounds in *S. dulcis* based on the pharmacological effects of the corresponding extracts of *S. dulcis*. In addition, compounds in *S. dulcis* that have clear antihyperglycemic and anti-hyperlipidaemia effects can be identified. The structure–activity relationships may be further explored based on their common chemical composition and pharmacological effects. Once the functional group is identified, substituent can potentially be modified to achieve higher pharmacological effectiveness. Furthermore, pharmacologists can continue to explore the specific targets of certain compounds in *S. dulcis*. For example, the targets of hypoglycemic effect may not be only those mentioned in this review, and new targets need to be further studied. Finally, if certain compounds in *S. dulcis* or their modified compounds with higher pharmacological activity are to be put into mass production in the pharmaceutical industry, the future researchers need to design a reasonable synthetic route. In short, *S. dulcis* is a well-used traditional herbal medicine, and perhaps new targets for the treatment of metabolic syndrome can be explored from the chemicals in it in the future.

Author contributions

Zikang Jiang and Lei Wen: concept development idea generation, literature collection and evaluation, manuscript preparation and editing, conduction of pharmacological effects, and analyzing their chemicals substances of *S. dulcis.*

Jinghui Sung: conduction of pharmacological effects analyses, associated with their effect on metabolic therapy, analysis results discussion, draft manuscript preparation, and editing.

Xuyun Wang, Yangyang Zhang, Yaomiao Wang, and Haifeng Zhou: pharmacological effects and their chemicals substances of *S. dulcis* analyses.

Conflicts of interest

There is no conflict to declare.

Notes and references

1 K. Masaru, H. Toshimitsu, A. Munehisa and M. H. Naokata, *Phytochemistry*, 1988, **27**(11), 3709–3711.
2 M. Silink, *Endocrinology*, 2011, **2007**(1), 12–14.
3 M. R. Mishra, R. K. Behera, S. Jha, A. K. Panda, A. Mishra, D. K. Pradhan and P. R. Choudary, *Int. J. Phytomed.*, 2011, **3**, 422–438.
4 G. Pamunuwa, D. N. Karunaratne and Y. Waisundara Viduranga, *Evid.-Based Complementary Altern. Med*, 2016, 8243215.
5 K. Hasui, J. Wang, X. Jia, M. Tanaka, T. Nagai, T. Matsuyama and Y. Eizuru, *Acta Histochem. Cytoc.*, 2011, **44**(3), 119–131.
6 C. Kamperdick, T. P. Lien, T. V. Sung and G. Adam, *Pharmazie*, 1997, **52**(12), 965–966.
7 M. Babincova, K. Schronerova and P. Sourivong, *Fitoterapia*, 2008, **79**(7–8), 587–588.
8 W. H. Wu, T. Y. Chen, R. W. Lu, S. T. Chen and C. C. Chang, *Phytochemistry*, 2012, **83**, 110–115.
9 W. Wankhar, S. Srinivasan, R. Rajan and S. Rathinasamy, *J. Appl. Pharmaceut. Sci.*, 2015, **5**(7), 029–034.
10 N. N. T. Tin, N. D. T. Truc, H. T. T. Hang, P. T. N. Trinh, T. D. Lam, L. T. Dung, *2nd International Conference on Mechanical Engineering and Applied Composite Materials*, Iop Publishing Ltd, Bristol, 2019.
11 S. M. D. Freire, L. M. B Torres, C. Souccar and A. J. Lapa, *J. Pharm. Pharmacol.*, 1996, **48**(6), 624–628.
12 M. Kawasaki, T. Hayashi, M. Arisawa, N. Morita and L. H. Berganza, *Phytochemistry*, 1988, **27**(11), 3709–3711.
13 T. Hayashi, M. Kishi, M. Kawasaki, M. Arisawa, N. Morita and L. H. Berganza, *J. Nat. Prod.*, 1988, **51**(2), 360–363.
14 Y. Li and Y. Ohizumi, *Yakugaku Zasshi*, 2004, **124**(7), 417–424.
15 Q. Liu, Q. M. Yang, H. J. Hu, L. Yang, Y. B. Yang, G. X. Chou and Z. T. Wang, *J. Nat. Prod.*, 2014, **77**(7), 1594–1600.
16 K. I. Sinan, K. Bene, G. Zengin, A. Diuzheva, J. Jeko, Z. Cziaky, C. M. N. Picot-Allain, A. Mollica, K. R. engasamy and M. F. Mahomoodally, *Int. J. Environ. Health Res.*, 2019, **31**(3), 285–297, Ahead of Print.
17 H. Alkhalidy, W. Moore, Y. Wang, J. Luo, R. P. McMillan, W. Zhen, K. Zhou and D. Liu, *Molecules*, 2018, **23**(9), 2338.
18 X. Chen, X. Cai, R. Le, M. Zhang, X. Gu, F. Shen, G. Hong and Z. Chen, *Biochem. Biophys. Res. Commun.*, 2018, **496**(2), 245–252.
19 H. M. Eid and P. S. Haddad, *Curr. Med. Chem.*, 2017, **24**(4), 355–364.
20 A. Ghorbani, *Biomed Pharmacother.*, 2017, PMID: 29017142.
21 T. Hibi, Y. Imai, A. Senoo, K. Ohta and Y. Ukyo, *J. Gastroenterol.*, 2017, **52**, 1101–1111.
22 S. Raja Kumar, E. S. Mohd Ramli, N. A. Abdul Nasir, N. H. M. Ismail and N. A. Mohd Fahami, *Evid Based Complement Alternat Med*, 2019, 9752826.
23 P. M. Giang, P. T. Son, M. Katsuyoshi and O. Hideaki, *Chem. Pharm. Bull.*, 2006, **54**(4), 546–549.
24 S. Asano, M. Mizutani, T. Hayashi, N. Morita and N. Takeguchi, *J. Biol. Chem.*, 1990, **265**(36), 22167–22173.
25 C. Y. Zhang, L. Z. Chen, Y. Y. Li, N. Wei, L. Zhang, L. Dong, Y. Zhang and X. P. Zhang, *Rec. Nat. Prod.*, 2020, **14**(5), 383–386.
26 W. Sun, Y. Zhang, Y. Li, L. Chen, L. Zhang, C. Zhang and X. Zhang, *Phytochem. Lett.*, 2020, **38**, 25–27.
27 R. Saikia, M. D. Choudhury, A. D. Talukdar and P. Chetia, *Asian J. Pharmaceut. Clin. Res.*, 2012, **5**(Suppl. 2), 153–158.
28 T. Hayashi, K. Okamura, M. Kakemi, S. Asano, M. Mizutani, N. Takeguchi, M. Kawasaki, Y. Tezuka, T. Kikuchi and N. Morita, *Chem. Pharm. Bull.*, 1990, **38**(10), 2740–2745.
29 M. Ahsan, S. K. N. Islam, I. Gray Alexander and H. Stimson William, *J. Nat. Prod.*, 2003, **66**(7), 958–961.
30 M. S. Islam, M. K. Ahmed, M. Raknuzzaman, M. Habibullah-Al-Mamun and S. Masunaga, *Arch. Environ. Contam. Toxicol.*, 2015, **68**(1), 92–106.
31 S. B. Mahato, M. C. Das and N. P. Sahu, *Phytochemistry*, 1981, **20**(1), 171–173.
32 R. Sharma Khaga, A. Adhikari, M. I. Choudhary, R. Sharma Khaga, K. Kalauni Surya, M. Hafizur Rahman, A. Hameed, A. Raza Sayed, J.-I. Miyazaki and M. I. Choudhary, *Phytotherapy research*, 2015, **29**(10), 1672–1675.
33 J. L. Ríos and S. Manez, *Plantamedica*, 2018, **84**(01), 8–19.
34 W. T. Wan, Y. Y. Ma, L. J. Xu and P. G. Xiao, *Zhongcaoyao*, 2015, **46**(16), 2492–2498.
35 J. Larsson, J. Gottfries, L. Bohlin and A. Backlund, *J. Nat. Prod.*, 2005, **68**(7), 985–991.
36 R. Khanra, S. Dewanjee, T. K. Dua and N. Bhattacharjee, *Biomed. Pharmacother.*, 2017, **88**, 918–923.
37 R. Khanra, N. Bhattacharjee, T. K. Dua, A. Nandy, A. Saha and J. Kalita, *Biomed. Pharmacother.*, 2017, **94**(2017), 726–741.
38 Q. Liang, J. Yang, J. He, X. Chen, H. Zhang, M. Jia, K. Liu, C. Jia, Y. Pan and J. Wei, *Biosci. Rep.*, 2020, **40**(4), BSR20192133.
39 S. Babu and S. Jayaraman, *Biomed. Pharmacother.*, 2020, **131**, 110702.
40 S. Datta, B. K. Sinha, S. Bhattacharjee and T. Seal, *J. Pharmacogn. Phytochem.*, 2018, **7**(2), 3963–3970.
41 M. Naveed, V. Hejazi, M. Abbas, A. A. Kamboh, G. J. Khan, M. Shumzaid, F. Ahmad, D. Babazadeh, X. FangFang, F. Modarresi-Ghazani, L. WenHua and Z. XiaoHui, *Biomed. Pharmacother.*, 2018, **97**, 67–74.
42 B. M. Bocco, R. A. Louzada, D. H. Silvestre, M. C. Santos, E. Anne-Palmer, I. F. Rangel, S. Abdalla, A. C. Ferreira, M. O. Ribeiro, B. Gereben, D. P. Carvalho, A. C. Bianco and J. P. Werneck-de-Castro, *J. Physiol.*, 2016, **594**(18), 5255–5269.
43 A. Pandi and V. M. Kalappan, *Mol. Biol. Rep.*, 2021, **2021**, PMID: 33988797.
44 J. Qiao, Z. Luo, S. Cui, H. Zhao, Q. Tang, C. Mo, X. Ma and Z. Ding, *J. Ind. Microbiol. Biotechnol.*, 2019, **46**(2), 147–157.
45 J. E. Beh, L. T. Khoo, J. Latip, M. P. Abdullah, N. B. M. Alitheen, Z. Adam, A. Ismail and M. Hamid, *J. Ethnopharmacol.*, 2013, **150**(1), 339–352.

46 O. M. Zabad, Y. A. Samra and A. E. Laila, *Life Sci.*, 2019, **238**, 116965.
47 A. Farshad, B. M. Razavi and H. Hosseinzadeh, *Phytother Res.*, 2020, **34**(4), 729–741.
48 K. Wangsa, I. Sarma, P. Saikia, D. Ananthakrishnan, H. N. Sarma and D. Velmurugan, *J. Reproduction Infertil.*, 2020, **21**(4), 247–258.
49 K. M. Nkembo, J. B. Lee and T. Hayashi, *Chem. Pharm. Bull.*, 2005, **53**(1), 780–782.
50 L. Pari and M. Latha, *BMC Compl. Alternative Med.*, 2004, **4**, 16.
51 M. Latha, L. Pari, S. Sitasawad and R. Bhonde, *J. Biochem. Mol. Toxicol.*, 2004, **18**(5), 261–272.
52 N. H. Parikh, P. K. Parikh and C. Kothari, *Chin. J. Nat. Med.*, 2014, **12**(5), 335–344.
53 R. Saikia, M. D. Choudhury, A. D. Talukdar and P. Chetia, *Asian J. Pharmaceut. Clin. Res.*, 2012, **5**(Suppl. 2), 153–158.
54 M. Latha and L. Pari, *Braz. J. Med. Biol. Res.*, 2004, **37**(4), 577–586.
55 M. Latha, L. Pari, S. B. Sandhya and R. Bhonde, *Life Sci.*, 2004, **75**(16), 2003–2014.
56 L. Pari and M. Latha, *Gen. Physiol. Biophys.*, 2005, **24**(1), 13–26.
57 A. Hameed, M. Hafizur Rahman, M. I. Khan, A. Jawed, S. Siddiqui, F. Khan, H. Wang, M. Zhao, K. Matsunaga, T. Izumi, A. Adhikari and R. Sharma Khaga, *Eur. J. Pharmacol.*, 2019, **858**, 172514.
58 R. Sharma Khaga, A. Adhikari, M. I. Choudhary, R. Sharma Khaga, K. Kalauni Surya, M. Hafizur Rahman, A. Hameed, A. Raza Sayed, J.-I. Miyazaki and M. I. Choudhary, *Phytotherapy researchPTR*, 2015, **29**(10), 1672–1675.
59 V. J. Sharma and U. D. Shah, *Int. J. ChemTech Res.*, 2010, **2**(1), 214–218.
60 P. Geethi and K. D. Nedra, *Evid.-Based Complementary Altern. Med.*, 2016, **2016**, 8243215.
61 J. E. Beh, J. Latip, M. P. Abdullah, A. Ismail and M. Hamid, *J. Ethnopharmacol.*, 2010, **129**(1), 23–33.
62 P. R. D. Perera, S. Ekanayake and K. Ranaweera, *Int. J. Appl. Chem.*, 2015, **2015**, 519–524.
63 L. Pari and M. Latha, *J. Med. Food*, 2006, **9**(1), 102–107.
64 S. P. A. Senadheera, S. Ekanayake and C. Wanigatunge, *BMC Compl. Alternative Med.*, 2015, **15**, 410.
65 S. M. Freire, L. M. Torres, N. F. Roque, C. Souccar and A. J. Lapa, *Mem. Inst. Oswaldo Cruz*, 1991, **86**(Suppl 2), 149–151.
66 S. M. Freire, J. A. da Silva Emim, A. J. Lapa, C. Souccar and S. M. d. F. Freire, *Phytother Res.*, 1993, **7**(6), 408–414.
67 J. C. Tsai, W. H. Peng, T. H. Chiu, S. C. Lai and C. Y. Lee, *Am. J. Chin. Med.*, 2011, **39**(5), 943–956.
68 J. Ofori-Amoah and G. A. Koffuor, *Pharmacologia*, 2015, **6**(8), 337–346.
69 P. Libby, P. M. Ridker and G. K. Hansson, *Nature*, 2011, **473**(7347), 317–325.
70 N. E. J. Orhue and E. A. C Nwanze, *Afr. J. Biotechnol.*, 2006, **5**(10), 883–887.
71 S. S. Nambiar, N. P. Shetty, P. Bhatt and B. Neelwarne, *Phcog. Mag.*, 2014, **10**(Suppl 2), S240–S248.
72 M. V. V. Lima, A. d. O. Freire, E. L. F. Sousa, A. A. M. Vale, A. J. O. Lopes, C. C. Vasconcelos, M. V. V. Lima-Aragao, H. O. Serra, R. N. M. G. Liberio, A. P. Silva de Azevedo dos Santos, G. E. B. Silva, C. Quintino da Rocha, F. C. V. M. Lima, M. d. S. d. S. Cartagenes and J. B. S. Garcia, *Molecules*, 2019, **24**(19), 3474.
73 The 168th Hospital of PLA, *Infection Department of 168 Hospital of Chinese people's Liberation Army*, 16th hospital of the Chinese People's Liberation, Army, 73, 1976, in Chinese.
74 J. C. Tsai, W. H. Peng, T. H. Chiu, S. C. Huang, T. H. Huang, S. C. Lai, Z. R. Lai and C. Y. Lee, *Am. J. Chin. Med.*, 2010, **38**(4), 761–775.
75 J. Paysant, P. Sansilvestri-Morel, E. Bouskela and T. J. Verbeuren, *Int. Angiol.*, 2008, **27**(1), 81–85.
76 T. K. Praveen, S. Dharmaraj, J. Bajaj, S. P. Dhanabal, S. Manimaran, M. J. Nanjan and R. Razdan, *Indian J. Pharmacol.*, 2009, **41**(3), 110–114.
77 I. Bulama, H. T. Kabara and A. Zarami, *Comp. Clin. Pathol.*, 2020, **29**, 807–813.
78 M. A. Adaikpoh, N. E. J. Orhue and I. Igbe, *Afr. J. Biotechnol.*, 2007, **6**(10), 1192–1196.
79 W. Wankhar, S. Srinivasan, R. Rajan and R. Sheeladevi, *J. Biomed. Res.*, 2017, **31**(2), 143–153.
80 W. D. Ratnasooriya, J. Jayakody, G. A. S. Premakumara and E. Ediriweera, *Fitoterapia*, 2005, **76**(2), 220–222.
81 Y. Coulibaly Ahmed, M. Kiendrebeogo, G. Kehoe Patrick, A. E. D. Sombie Pierre, E. Lamien Charles, F. Millogo Jeanne and G. Nacoulma Odile, *J. Med. Food*, 2011, **14**(12), 1576–1582.
82 A. Elayaraja and S. Abdul Rahaman, *J. Pharmaceut. Sci. Res.*, 2012, **4**(2), 1724–1727.
83 N. Chana, P. Supaphon and A. Phongdara, *Songklanakarin J. Sci. Technol.*, 2019, **41**(1), 246–253.
84 M. M. A. R. Moniruzzaman and A. Ferdous, *J. Evidence-Based Complementary Altern. Med.*, 2015, **2015**, 873954.
85 T. A. Abere, C. J. Okoye, F. O. Ahoeryo, *et al.*, *BMC Complementary Altern. Med.*, 2015, **15**, 414.
86 B. Madakkannu and R. Ravichandran, *Toxicol. Rep.*, 2017, **4**, 484–493.
87 R. Ahemd, H. D. Nuhu, H. Ibrahim, *et al.*, *Trop. J. Nat. Prod. Res.*, 2019, **3**(3), 64–70.
88 C. O. Esume, A. O. Opajobi, A. Osasuyi, O. O. Ebong and A. K. Osakwe, *Biomed. Pharmacol. J.*, 2011, **4**(1), 11–19.
89 F. A. van de Laar, P. L. Lucassen, R. P. Akkermans, E. H. van de Lisdonk, G. E. Rutten and C. van Weel, *Diabetes Care*, 2005, **28**(1), 154–163.
90 M. C. Thomas, K. A. Jandeleit-Dham and C. Tikellis, *PPAR Res.*, 2012, **2012**(2), 456529.
91 S. Y. Chow, S. M. Chen, C. M. Yang and H. Hsu, *J. Formosan Med. Assoc.*, 1974, **73**, 729–739.
92 L. Pari, M. Latha and C. A. Rao, *J. Basic Clin. Physiol. Pharmacol.*, 2004, **15**(3–4), 223–240.
93 M. Latha, L. Pari, K. M. Ramkumar, P. Rajaguru, T. Suresh, T. Dhanabal, S. Sitasawad and R. Bhonde, *Nat. Prod. Res.*, 2009, **23**(16), 1528–1540.
94 R. Rajan, M. Vedi, B. Sridharan, M. Himaja, E. P. Sabina and N. A. N. Raj, *Int. J. Phytomed.*, 2014, **6**(4), 617–624.