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Review Article

Current Insight on *Siraitia grosvenorii* Flavonoids Extraction Process and its Bioactivity Characteristic: A Review

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ABSTRACT

The *Siraitia grosvenorii* is a Chinese herb with various bioactive properties that has been widely used as a culinary ingredient and in traditional medicine. Flavonoids are among the important bioactive compounds in *S. grosvenorii*, which contribute significantly to the biological activity of *S. grosvenorii*. *S. grosvenorii*-flavonoids have been reported to possess various biological and pharmacological activities, including antioxidant, antibacterial, anti-inflammatory, hypolipidemic, and anti-diabetic, which are important for human health. Based on previous reports, the structure, extraction technology, biological activity and further development regarding *S. grosvenorii*-flavonoids are reviewed in this paper, providing appropriate insights and references for future development of *S. grosvenorii*-flavonoids.

Keywords: Bioactivity, extraction process, flavonoids, pharmacological activity, *Siraitia grosvenorii*

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INTRODUCTION

The continuous development and improvement of science and technology provide people with production and life conveniences but are also fraught with innumerable risks and challenges. The potential risks of chemical food additives and drug resistance are among today's scientific challenges (Irfan et al., 2022;

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Moudaka et al., 2023; Najm et al., 2022). To solve these problems, researchers are searching for new, safer, and more appropriate natural bioactive compounds as substitutes (Zang et al., 2022). *Siraitia grosvenorii* (*Luo Han Guo*) is a Cucurbitaceae herb mainly distributed in China's tropical and subtropical regions (Figure 1). The Chinese explored, applied, and recorded its medicinal potential more than 300 years ago (Gong et al., 2019). Presently, *S. grosvenorii* fruit is widely used as a food sweetener (Li, Li et al., 2022) and supplement ingredients (Abdel-Hamid et al., 2020) due to its natural sweet, low-calorie glycosides, which are regarded as an ideal new sugar source for patients with diabetes and obesity (Thakur et al., 2022). Numerous substances, including a wide variety of triterpenoids and flavonoids, as well as amino acids and two types of polysaccharides, have been isolated from *S. grosvenorii* to date (Duan et al., 2023; Gong et al., 2022), adding to its value for future development and use. Table 1 displays some common compounds and their activities in *S. grosvenorii* extracts.

Flavonoids are a class of bioactive molecules with various phenolic structures in plants' fruits, roots, stems, leaves, and flowers, among other parts of *S. grosvenorii.* Due to their antioxidant, anti-inflammatory, and anticancer properties, as well as their ability to regulate the functions of important cellular enzymes, they are regarded as essential components in numerous contemporary food, pharmaceutical, and cosmetic applications (Shen et al., 2022; Čižmárová et al., 2023). Additionally, with the rise of numerous cardiovascular, cerebrovascular, and immune diseases in recent years, flavonoid research and application in the management of numerous cerebrovascular diseases and immune deficiency diseases has garnered particular interest (Barreca et al., 2023; Keylani et al., 2023). It was discovered that flavonoids, mainly flavonoids and flavonols, are one of the primary active components

Figure 1. The distribution of *Siraitia grosvenorii* in China

Table 1
Some common compounds and their activities in S. grosvenorii *extracts*

Classification	Compounds	Plant Part	Bioactivities	*In vivo/ In vitro*	References
Polysaccharide	SGP-1	Fruit	Anti-oxidant	*In vitro*	Zhu et al., 2020
	SGP-1-1	Fruit	Anti-oxidant; Hypoglycemic	*In vitro*	Gong et al., 2022
Triterpenes	Mogrol	Fruit	Anti-inflammatory; Anti-colitis; Anti-cancer; Anti-osteoporosis; Anti-proliferative	*In vivo; In vitro*	Li, Liu et al., 2022; Chen et al., 2022; Song et al., 2022
	11-oxo-mogrol	Fruit	Induced neuronal damages	*In vitro*	Ju et al., 2020
	Siamenoside I	Fruit	Anti-diabetic; Anti-alzheimer	*In vivo; In vitro*	Liu et al., 2019; Cai et al., 2023
	Mogroside III	Fruit	Anti-diabetic; Anti-alzheimer	*In vivo; In vitro*	Liu et al., 2019; Cai et al., 2023
	Mogroside IV	Fruit	Anti-diabetic; Anti-alzheimer	*In vivo; In vitro*	Liu et al., 2023; Cai et al., 2023
	Mogroside V	Fruit	Anti-oxidant; Anti-inflammatory; Against neuronal damages; Anti-diabetic	*In vivo; In vitro*	Luo et al., 2022; Shen et al., 2022; Liu et al., 2023
	Mogroside IIE	Fruit	Anti-lung injury; Anti-inflammatory	*In vivo*	Lü et al., 2024
	Mogroside IIIE	Fruit	Anti-inflammatory; Anti-fibrosis	*In vivo; In vitro*	Yanan et al., 2023
	β-amyrin	Fruit	Therapeutic intervention in tuberculosis	*In vitro; In silico*	Beg et al., 2022
Flavonoids	Afzelin	Fruit	Anti-bacterial; Anti-oxidant; Anti-tumor; Anti-oxidant	*In vivo; In vitro*	Wang et al., 2015; Akter et al., 2022
	Kaempferol	Flower; Leaves	Anti-bacterial; Anti-oxidant; Hypoglycemic; Anti-obesity;	*In vitro*	Li et al., 2018; Bian et al., 2022
	Kaempferol-7-O-α-L-rhamnopyranoside	Fruit; Flower; Leaves	Anti-oxidant	*In vivo; In vitro*	Fang et al., 2017; Mo and Li, 2009
	Kaempferitrin	Leaves; Fruit	Anti-bacterial; Anti-oxidant; Anti-tumor	*In vivo; In vitro*	Wang et al., 2015; Su et al., 2023)

Table 1 (*continue*)

Classification	Compounds	Plant Part	Bioactivities	*In vivo/ In vitro*	References
	Grosvenorine	Flower; Leaves; Fruit	Anti-hyperglycemic; Anti-inflammatory	*In vivo; In vitro*	Sung et al., 2020; Zhang et al., 2020
	7-methoxyl-kaempferol-3-O-α-L-rhamnopyranoside	Flower	Anti-oxidant	*In vivo*	Mo and Li, 2009
	7-methoxy-kaempferol-3-O-β-D-glucopyranoside	Flower	Anti-oxidant; Anti-hyperglycaemic	*In vivo*	Janibekov et al., 2018; Mo and Li, 2009
	Aloe-emodin	Leaves	Anti-bacterial; Cerebroprotective	*In vitro; In silico; In vivo*	Yang et al., 2016; Pasala et al., 2022
	Aloe-emodin acetate	Leaves	Anti-bacterial; Cerebroprotective	*In vitro; In silico; In vivo*	Yang et al., 2016; Pasala et al., 2022
	p-Hydroxybenzoic Acid	Leaves			Yang et al., 2016
	Rutin	Fruit			Fang et al., 2017
Others	Genistein	Fruit			Fang et al., 2017
	Siraitic acid II	Root	Anti-diabetic	*In vitro*	Lu et al., 2023
	Cucurbitacin B	Root	Anti-diabetic	*In vitro*	Lu et al., 2023
	(-)-lariciresinol	Root	Anti-diabetic	*In vitro*	Lu et al., 2023
	Siraitic Acid F	Root			Lu et al., 2023
	Cucurbitacin B	Root			Lu et al., 2023
	23,24-Dihydrocucurbitacin B	Root			Lu et al., 2023

of *S. grosvenorii*. The *S. grosvenorii*-flavonoids, in contrast to mogrosides, are present not only in the fruit but also in the leaves, roots, and flowers.

These flavonoids exhibit potent antioxidant, antibacterial, anticancer, and hypoglycemic properties (Lu et al., 2023; Wang et al., 2015; Wu et al., 2022). Prior research on the flavonoids from *S. grosvenorii* focused primarily on extraction methods, structural characterization, and in vitro activity detection, while in vivo activity, mechanism of action, and clinical applications were the subject of relatively few studies. It is necessary to conduct exhaustive research on these compounds to broaden and extend the applicability field and direction of the *S. grosvenorii* extract. In this review, the extraction processing, chemical structure, pharmacological activity, and future development of *S. grosvenorii*-flavonoids are discussed to provide a reference as well as the future direction for the in-depth research and application of active compounds in *S. grosvenorii*.

THE EXTRACTION PROCESSING

Extraction Method

Extraction of components is frequently the initial step in compound research. Since various extraction techniques and extraction procedures have a significant impact on the extraction efficiency of compounds and the subsequent investigation of chemicals, choosing the best extraction methods and conditions is crucial. *S. grosvenorii*-flavonoids are primarily extracted using organic solvent extraction, ultrasound-assisted extraction (UAE), microwave-assisted extraction (MAE), and enzyme-assisted extraction (EAE). Table 2 displays the procedures utilized to extract *S. grosvenorii-flavonoids.*

Solvent extraction transfers a target substance from one solvent to another by utilizing various substances' different partition coefficients and solubilities. There are numerous examples of solvent extraction of flavonoids. For example, In the latest study, Lu et al. (2023) extracted several active flavonoids from the roots of *S. grosvenorii* with 75% ethanol. Wuttisin and Boonsook (2019) extracted total flavonoids from *S. grosvenorii* using distilled water, n-hexane, ethyl acetate, 95% ethanol, and propylene glycol and compared the effect of different solvents on the extraction rate. The results revealed that using distilled water as the extractant agent yielded the highest extraction rate.

Some organic components in solid or semi-solid substances can be extracted with the help of a microwave by using the electromagnetic field to pull them away from the matrix. This method has several advantages over conventional extraction techniques, including high efficiency, energy efficiency, safety, and environmental protection. Zhang et al. (2013) used microwave extraction techniques to extract flavonoids from S. grosvenorii flowers. They found that the following process parameters worked best: solvent: 60% ethanol solution; solid-liquid ratio: 1: 30 (g/mL); microwave power: 350 W; radiation time: 20 min. Under this condition, the yield of flavonoids in *S. grosvenorii* flowers can reach 7.6%. In addition,

Table 2
The methods to extract S. grosvenorii-*flavonoids*

Method	Solvent	Temperature (℃)	Time (min)	Solid-liquid Ratio (g/ml)	Other	References
Soxhlet Extraction	70% Ethanol	25°C		1:10		Lu et al., 2023
Organic Solvent extraction	Distilled water	80°C	60			Wuttisin & Boonsook, 2019
	n-hexane	25°C	1440			
	Ethyl Acetate	25°C	1440			
	95% Ethanol	25°C	1440			
	Propylene Glycol	25°C	1440			
Microwave-assisted Extraction (MAE)	60% Ethanol		20	1:30	Microwave Power:350 W	Zhang et al., 2013
Ultrasonic-assisted Extraction (UAE)	67% Ethanol		43	1:15	Ultrasonic Power: 208 W	Zhang et al., 2016
Subcritical Fluid Extraction	Sub-critical water; 15% Ethanol	140℃	20	1:30	Pressure: 4 MPa	Xu et al., 2017
Enzyme Assisted Extraction (EAE)	Ethanol; Petroleum benzine; ethyl acetate	65℃	80	1:8; 3:1; 2:1	Cellulase (50 U/ml); pH 5.2	Wang et al., 2006

Zhang et al. (2016) used ultrasonic-assisted extraction technology to extract total flavonoids in the flowers of *S. grosvenorii*, optimized the extraction process through orthogonal experiments, and finally determined the optimal process conditions: the concentration of ethanol was 67%, the extraction time was 43 min, the ultrasonic power was 208 W, and the ratio of solvent-to-solid was 1:15 (g/mL). Under these conditions, the extraction rate of total flavonoids could reach 6.5%.

Subcritical water extraction (SWE) technology is a process in which the raw materials are put into subcritical fluids for extraction according to the principle of similar compatibility, and the effective components in the materials are extracted under different conditions. Xu et al. (2017) used subcritical extraction technology to extract the active substances in *S. grosvenorii* and determined the optimal process conditions of the method: the extraction temperature was 140°C, the ethanol addition was 15%, and the extraction time was 20 min. Under the extraction conditions, the content of flavonoids was up to 11.90 mg/g, and the antioxidant activity of the extracts was found to be optimal. Enzyme-assisted extraction is a method that uses active enzymes to hydrolyze certain substances with specific structures to obtain target substances. Currently, this method is mostly used

in the auxiliary production and extraction of mogrosides, while flavonoid extraction in *S. grosvenorii* is rarely mentioned. However, as early as 2006, Wang et al. used the enzyme (cellulase)-solvent method to extract flavonoids from *S. grosvenorii* and found that the optimal extraction conditions: cellulase concentration 50 U/ml, pH 5.2, temperature 65°C, time 80 min.

In conclusion, different extraction conditions have different effects on the extraction rate of *S. grosvenorii*-flavonoids, with the most influential parameters being extraction temperature, solid-liquid ratio, extraction duration, and extraction concentration.

Isolation and Purification Method

The process of isolating a substance from a mixture is isolation and purification. Typically, flavonoids are purified and separated using column chromatography, solution extraction, and supercritical fluid extraction. Table 3 lists the techniques for isolating and purifying *S. grosvenorii*-flavonoids.

Table 3
The methods for the isolation and purification of S. grosvenorii-*flavonoids*

Method	Isolated flavonoid compounds	References
HPLC	Kaempferitrin; Afzelin; a-Rhamnoisorobin; Kaempferol	Wang et al., 2015
UF-HPLC; MCI CHP-20P Column Chromatography; HSCCC	3,4′-dimethoxy-4,9,9′-trihydroxy-benzofuranolignan-7′-ene; 23,24-dihydrocucurbitacin F; 23,24-dihydrocucurbitacin F-25-acetate	Lu et al., 2023
UHPLC	Kaempferol-3-O-α-L-[4-O-(4-carboxy-3-hydroxy-3-methylbutanoyl)]-rhamnopyranoside-7-O-α-L-rhamnopyranoside; Grosvenorine; Kaempferitrin; Afzelin	Lu et al., 2020
Unitary-C18 column	Quercetin; Rutin; Neohesperidin; Naringin; kaempferol O-glycoside-rhamcoside; quercetin O-arabinoside-O'-glycoside-rhamnoside; 4′-methoxyl-kaempferol	Qing et al., 2017

Column chromatography is one of the most traditional and widespread separation techniques. This method is a separation procedure in which the components in the mixture are separated from each other by repeated distribution in the stationary phase and mobile phase with varying partition coefficients. Based on the different adsorbents, the method is mostly made up of polyamide column chromatography, silica gel column chromatography, dextran gel column chromatography, the macroporous resin adsorption method, and high-performance liquid chromatography (HPLC). The HPLC was used to separate the flavonoids from the biologically active kaempferitrin, afzelin, -a-rhamnoisorobin, and kaempferol in *S. grosvenorii* (Wang et al., 2015). In a recent study, Lu et al. (2023) used ultrafiltration (UF) combined with high-performance liquid chromatography (HPLC) to target α-glucosidase inhibitors from *S. grosvenorii* roots.

Also, researchers used ultra-high performance liquid chromatography (UHPLC) with electrospray ionization quadrupole time-of-flight mass to separate and identify 34 flavonoids from the leaves of *S. grosvenorii*. It included 19 kaempferol O-glycosides, 4 quercetin O-glycosides, 6 flavanone derivatives, and 5 polymethoxy-flavones (Lu et al., 2020). Qing et al. (2017) isolated 53 flavonols and flavonols glycosides from *S. grosvenorii* by using a unitary C18 column (HPLC). At the same time, two isoflavones (4',7-dihydroxyisoflavone (Daidzein) and 4',5,7-trihydroxyisoflavone (Genistein) were isolated and purified from the *S. grosvenorii* extracts using C-18 column chromatography (Chaturvedula & Prakash, 2013).

THE COMPONENTS DISTRIBUTION AND STRUCTURE

The Components Distribution

It has been discovered that the fruit, leaves, stems, and flowers of *S. grosvenorii* contain a significant quantity of flavonoids, with the stems, leaves, and flowers containing more. Some parts of *S. grosvenorii* used in the industries are shown in Figure 2.

Wuttisin and Boonsook (2019) extracted the flavonoids from *S. grosvenorii* using various solvents (distillate water, propylene glycol, 95% ethanol, ethyl acetate, and hexane). The results showed that compared with other solvent extracts, the total flavonoid content of the distilled water extract was up to 25.229±0.904 μg QE/mg solid crude extract. However, the 95% ethanol extract had the highest polyphenol content. At the same time, DPPH and ABTS methods were used to evaluate the antioxidant activity of *S. grosvenorii* extracts, and it was found that the distilled water extract had the most significant antioxidant activity, suggesting that the antioxidant activity of *S. grosvenorii* extracts may be associated with the presence of flavonoids.

In addition, Metabolic profiling analysis was used to analyze and identify the compositional characteristics of green and yellow fruits of *S. grosvenorii* (Fang et al., 2017). The results revealed that yellow fruits contained fewer flavonoids than green fruits and that the peel contained more flavonoids than the fruit. Zhang et al. (2013) used HPLC-TOF-MS combined with the PCA pattern recognition method to compare and analyze the chemical

(a) (b) (c)

Figure 2. Parts of *S. grosvenorii.* (a) leave, (b) ripe fruit, (c) dried fruit powder of *S. grosvenorii*

components of different parts of *S. grosvenorii*. The analysis showed that the chemical components of the fruit and pericarp were similar but significantly different from those of the leaf and stem. Mogrosides are markers of *S. grosvenorii* fruit, and five flavonoid glycosides are selected as leaf and stem markers. In addition, Rao et al. (2012) used the spectrophotometer method and kaempferin as a control to measure the flavonoid content in the fruit, stem, and leaf extracts of *S. grosvenorii*. The results showed that the content of flavonoid in the stem and leaf (345.11 mg/g) was much higher than that in the fruit (13.89 mg/g), which provides an experimental basis for the development and utilization of *S. grosvenorii* branches and leaves.

The Structure and Composition

The *S. grosvenorii*-flavonoids are mostly found as flavones and flavonols, most of which are compounds with kaempferol or quercetin aglycones (Wu et al., 2022), and the composition and structure of flavones are also related to the plant portions in which they are found. The types and structures of flavonoids isolated from different parts of *S. grosvenorii* also vary. A variety of flavonoids have been isolated from the flowers of *S. grosvenorii*, including kaempferol, 7-methoxy-kaempferol-3-O-β-D-glucopyranoside, kaempferol-3-O-L-rhamnoside-7-O-[β-D-glucosyl-(1-2)-α-L-rhamnoside]-3-O-L-rhamnoside and 7-methoxyl-kaempferol-3-O-α-L-rhamnopyranoside (Mo & Li, 2009). In addition, kaempferitrin, kaempferol-7-O-α-L-rhamnopyranoside, kaempferol-3,7-O-L-dirhamnopyranoside, aloe emodin acetate, aloe emodin, afzelin, and quercetin were also isolated from fruits and leaves (Yang et al., 2016; Lu et al., 2020). The composition of different parts of *S. grosvenorii* and the structure of *S. grosvenorii*-flavonoids are shown in Table 1 and Figure 3, respectively.

BIOLOGICAL ACTIVITIES OF FLAVONES FROM *S. GROSVVENOORII*

Traditional Chinese medicine believes that *S. grosvenorii* has various physiological functions, including lung clearing, phlegm clearing, and diarrhea stopping, which can treat and relieve cough, sore throat, constipation, and other symptoms (Wu et al., 2022). Modern scientific research shows that different extracts from *S. grosvenorii* have different biological and pharmacological activities (Li, Li et al., 2022; Zhu et al., 2020).

Flavonoids have sparked interest as a natural active substance due to their high activity value. With a better understanding of this substance activity, its many biological activities, such as anticancer, anti-inflammation, anti-mutation, and antioxidant activity, have been developed and applied in a variety of fields (Mitra et al., 2022; Shen et al., 2022). Due to their antibacterial and antioxidant properties, flavonoids are commonly used in food safety and health disciplines as antioxidants and bacteriostats. Due to their unique bacteriostatic or insecticidal properties, flavonoids are also used in agriculture as insecticides. At the

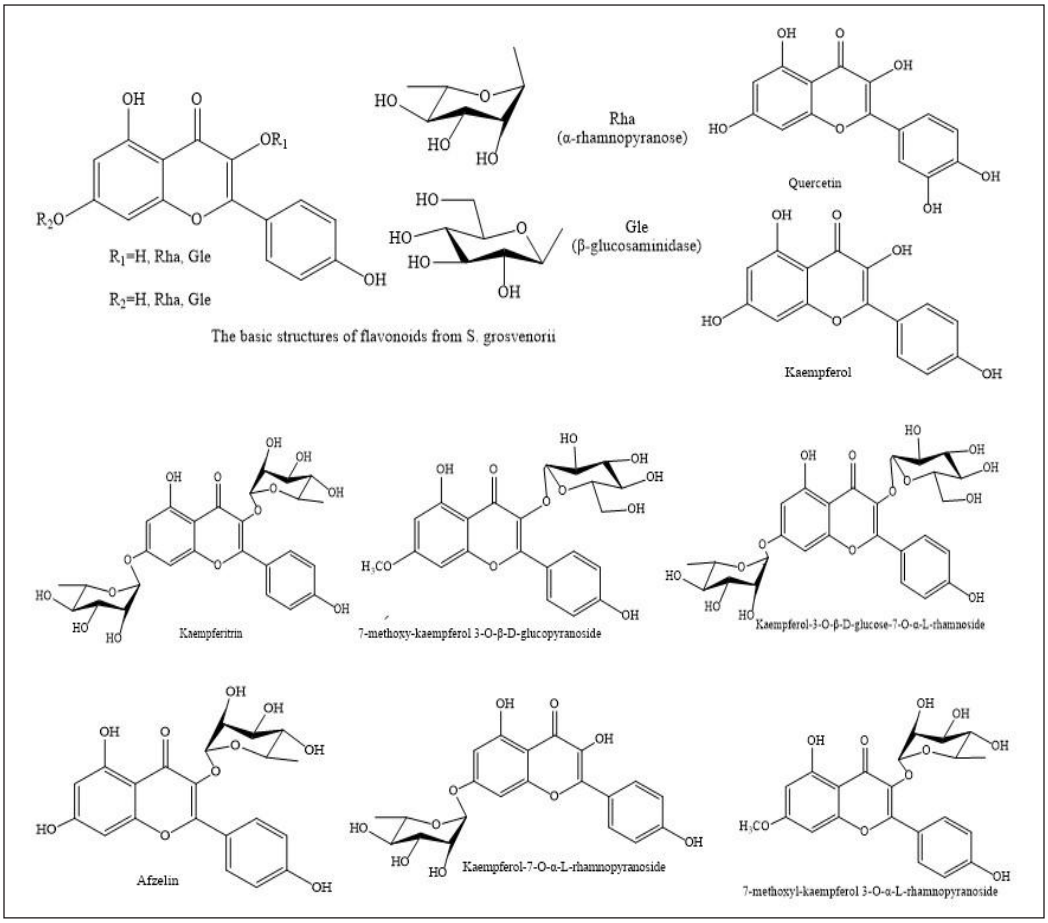

Figure 3. The structures of flavonoids extracted from *S. grosvenorii*

same time, flavonoids have been developed and used as various drugs in human medicine due to their unique medical activity, such as those for diabetes, cancer, anti-tumor therapy, and other drugs. The *S. grosvenorii*-flavonoids are a key component of the plant, and their diverse activities have been studied and reported. The biological activities of *S. grosvenorii*-flavonoids are listed in Table 1.

Antioxidant Activity

Free radicals and reactive oxygen species are well known for causing oxidation and damage to cell membranes, DNA, and/or proteins, which can have serious consequences for human health and cause a variety of diseases such as cancer, neurodegenerative diseases, cardiovascular disease, diabetes, and aging (Ooi et al., 2021). Researchers in the food and pharmaceutical fields are often looking for active compounds that can clear and slow this damage as antioxidant molecules (Azfaralariff et al., 2022). Experiments have confirmed

that the *S. grosvenorii*-flavonoids contain a large number of phenolic hydroxyl groups, which have a significant scavenging effect on α-diphenyl-β-picrylhydrazyl (DPPH) free radicals and 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonate) (ABTS) free radicals, and this effect is positively correlated with the concentration and action time of flavonoids. These studies have confirmed that the flavonoids extracted from *S. grosvenorii* are natural and effective free radical scavengers, which can be widely used in the food and pharmaceutical industries (Pan et al., 2012; Pandey & Chauhan, 2019).

Studies have found that compared with the propylene glycol and ethanol extracts of *S. grosvenorii*, the distilled water extract (polyphenols and flavonoids) of the substance had stronger antioxidant activity, and its α-diphenyl-β-picrylhydrazyl (DPPH) scavenging activity and 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonate) (ABTS) scavenging activity increased with the increase of its solvent polarity (Wuttisin & Boonsook, 2019). Moreover, some studies have detected the antioxidant activity of 5 flavonoid glycosides with different structures in the *S. grosvenorii* flower(kaempferol, kaempferol-7-α-L-rhamnopyranoside, 7-methoxyl-kaempferol-3-O-α-L-rhamnopyranoside, 7-methoxyl-kaempferol-3-O-β-D-glucopyranoside and 3-O-α-L-rhamnopyranosyl-kaemferol-7-O-[β-D-glucopyranosyl-(1-2)-α-L-rhamnopyranoside]), and found that kaempferol and kaempferol-7-α-L-rhamnoside showed well anti-diabetic activities and the 7, 3-hydroxyl group in the flavonoid structure was an important factor affecting its antioxidant activity (Mo & Li, 2009). Pan et al.(2012) studied the antioxidant activity of the alcoholic extract of *S. grosvenorii* leaves, and the results showed that the ethanol crude extract (SEE) of *S. grosvenorii* had similar antioxidant activity to butylated hydroxytoluene (BHT), and found that kaempferol-3-O-α-L-rhamnopyranosyl-7-O-[β-D-glucopyranosyl-(1-2)-O-L-rhamnoside], kaempferol-3-O-β-D-glucose-7-O-α-L-rhamnoside and quercetin were isolated from crude ethanol extract (SEE) showed significant scavenging free energy, which can provide corresponding scientific basis and guidance for the development and utilization of *S. grosvenorii* leaves. Similarly, a strong linear correlation was found between polyphenolic compounds (including flavonoids) and their antioxidant activity in the antioxidant activity of *S. grosvenorii* cultured cells, among which kaempferol-3-O-Glc-7-O-Rha played the most important antioxidant role (Liu et al., 2022).

Hypoglycemic Activity

Diabetes mellitus (DM) is a chronic disease characterized by metabolic disorders of the endocrine system (Yedjou et al., 2023). There are two types of diabetes mellitus: type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) (Sethupathi et al., 2023). The disease causes long-term damage to the living body's organs, resulting in dysfunction and failure, eventually leading to disability and premature death (Ibrahim et al., 2023; Kropp et al., 2023). This disease and its complications have caused serious distress to people and posed major economic challenges to society in both developing and developed countries.

Insulin and related reagents, biguanides, sulfonylureas, α-glucosidase inhibitors, thiazolidinediones, and dipeptidyl peptidase-IV inhibitors are some of the most commonly used diabetic drugs in clinical trials (Dahlén et al., 2022). However, these chemical drugs have several negative side effects, including adverse patient reactions and high costs. As a result, researchers are looking for low-cost natural active ingredients to develop and use as new anti-diabetic drugs. Natural active ingredients, such as flavonoids, terpenoids, and saponins, have been recognized as important sources of potent anti-diabetic drugs (Khuntia et al., 2022). These active ingredients often achieve anti-diabetic effects by increasing insulin secretion or reducing intestinal glucose absorption.

Increased precursors of advanced glycation end products (AGEs), elevated levels of diacylglycerol, and increased hexosamine pathway activity are some intracellular metabolic changes that typically lead to hyperglycemia and hyperlipidemia symptoms. These changes frequently result in tissue cell damage and diabetic complications. (Singh et al., 2022). Advanced glycation end products (AGEs) are crucial in developing diabetes and its side effects. Reducing the level of glycosylation and the production of advanced glycation end products is a feasible strategy for postponing or preventing diabetic complications because the formation of these compounds is generally increased in diabetic patients.

It has become an important testing point for many natural and pharmacological compounds being investigated for their potential therapeutic potential (Cheun-Arom & Sritularak, 2023). In addition, excessive ROS/RNS in the organism is also one of the main signs of hyperglycemia and hyperlipidemia, which are usually caused by the oxidation of glucose and free fatty acids in the cells suffering from the symptoms. Therefore, it is also one of the important factors to explore in the mechanism of diabetes (Singh et al., 2022). Part of the mechanism of flavonoids in diabetes is shown in Figure 4.

Previous studies on the hypoglycemic/anti-diabetic activities of *S. grosvenorii* extracts mainly focused on mogroside, while studies on the effects of flavonoids in *S. grosvenorii* extracts were rare. However, some studies have also found that the flavonoids in *S. grosvenorii* have hypoglycemic effects. Studies have found that the high dose of flavonoids from *S. grosvenorii* (80 mg/kg) could effectively reduce the blood glucose level of STZ-induced diabetic rats (from 22.68 ± 2.55 mmol/L to 10.63 ± 2.88 mmol/L). The medium dose of total flavonoids (40 mg/kg) could effectively reduce blood lipids (from 3.51 ± 0.53 mmol/L to 1.26 ± 0.37 mmol/L) in STZ-induced diabetic rats. Moreover, it was also found that the high dosage of total flavonoids (80 mg/kg) could significantly increase the activities of SOD and GSH-Px ($P < 0.01$) and the level of insulin ($P < 0.01$) and reduce the content of MDA ($P < 0.05$) in STZ-induced diabetic rats (Zheng et al., 2011).

Even though there have only been a small number of studies on the hypoglycemic effects of *S. grosvenorii*-flavonoids, earlier research has shown that these compounds significantly reduce sugar, inhibit a-glucosidase, and safeguard the pancreas. Additionally,

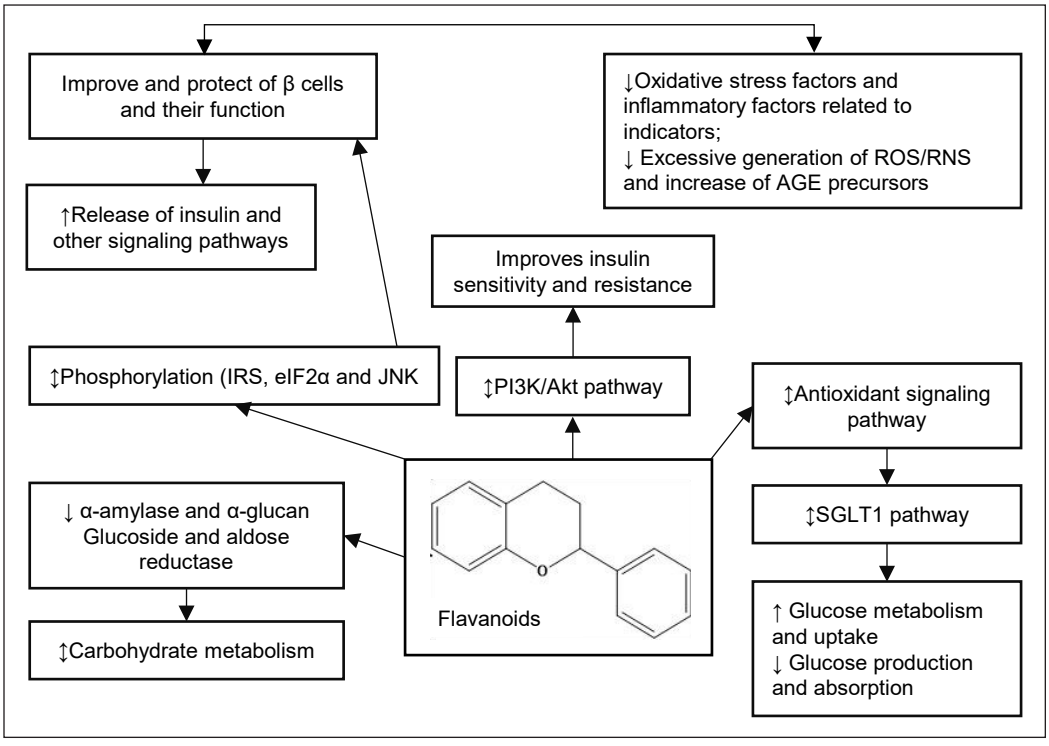

Figure 4. Part of the mechanism of flavonoids in diabetes (↑: increase, ↓: decrease and ↕: modulatory effect)

consuming more flavonoids can lower the risk of developing diabetes. Kaempferol, which is extracted from tea, cruciferous vegetables, grapefruit, and some edible berries, can achieve anti-diabetic effects by inhibiting hepatic gluconeogenesis, reducing Caspase-3 activity in β cells, and enhancing β cell survival, improving cAMP signaling (Alkhalidy et al., 2015; Alkhalidy et al., 2018; Sharma et al., 2020). The quercetin extracted from chokeberry, black currant, apple, and cherry can also achieve anti-diabetic effects by improving the AMPK pathway, inhibiting the expression of NF-kB and caspase-3, and protecting the function of pancreatic beta cells (PBC) (Dhanya et al., 2017; Li et al., 2020; Eid & Haddad, 2017). These studies may provide a useful foundation for future research and development into the anti-diabetic activity of flavonoids found in *S. grosvenorii.*

Antibacterial Activity

The widespread use of antibiotics has led to an increasing number of drug-resistant bacteria, so developing new and natural antibacterial drugs has become a hotspot in the research field (Huang et al., 2022; Shahid et al., 2022). The antibacterial properties of flavonoids have been demonstrated in several studies, and they have also been used to create new antibacterial agents and antibacterial medications. Flavonoids inhibit bacteria mainly by affecting biofilm formation, porin, permeability, and interaction with some key enzymes

(Shamsudin et al., 2022). At the same time, studies have also found that some flavonoids can combine with DNA helicase, thereby inhibiting its ATPase activity and achieving the antibacterial effect. Through structure-activity relationship studies, the antibacterial effect of flavonoids is shown to have a close relationship to the position of the hydroxyl group in the structure of the flavonoid (Adamczak et al., 2019).

Previous studies conducted via a simulated human gastrointestinal tract environment showed that grosvenorine and other metabolites (such as kaempferol, afzelin, a-rhamnoisorobin, and kaempferitrin) extracted from *S. grosvenorii* showed good antibacterial activity. In addition, these substances have higher antibacterial activity against Gram-positive bacteria than against Gram-negative bacteria. The MIC values against Gram-positive bacteria were all less than 70 mg/ml (Wang et al., 2015). Studies have shown that the active components of *S. grosvenorii*, which include kaempferol, had a clear bacteriostatic impact on spoilage bacteria isolated from sauced pork head meat, with *Proteus vulgaris* being the most significantly inhibited of the bacteria studied. (Li et al., 2018). Several investigations have indicated that total phenols and total flavonoids isolated from the roots of *S. grosvenorii* have a specific inhibitory effect on *Aspergillus* sp., *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Rhizopus* sp (Yang et al., 2022).

Anti-inflammatory Activity

Inflammation is a complex protective response produced by the body to eliminate harmful stimuli such as pathogens, irritants, or damaged cells, and it is implicated in many diseases such as diabetes, asthma, cardiovascular disease, and cancer (Kaur & Singh, 2022; Razak et al., 2023). Although anti-inflammatory drugs can effectively treat diseases, their damage and side effects on the body cannot be ignored (Bibbins-Domingo, 2016). As a result, using natural compounds derived from medicinal plants to treat inflammation has become popular, with polyphenols and flavonoids receiving particular attention due to their anti-inflammatory properties (Zhang et al., 2022). The anti-inflammatory effects of flavonoids are mainly exerted by inhibiting the activities of a variety of enzymes and the production of inflammatory mediators (Suriyaprom et al., 2023; Liu et al., 2023). The anti-inflammatory effects of flavonoids are shown in Figure 5.

Studies have found that kaempferol and quercetin can achieve anti-inflammatory effects by regulating the inducible nitric oxide synthase (iNOS), inhibiting the expression of lipoxygenase (LOX), and cyclooxygenase-2 (COX-2) as well as regulating the gene expression of inflammatory molecules (Septembre-Malaterre et al., 2022; Pal et al., 2023). In addition, it has also been found that kaempferin extracted from the residual extract of *S. grosvenorii* can exert anti-inflammatory activity by inhibiting the expression of TNF-α/IFN-γ-induced filaggrin and blocking MAPK activation (Sung et al., 2020).

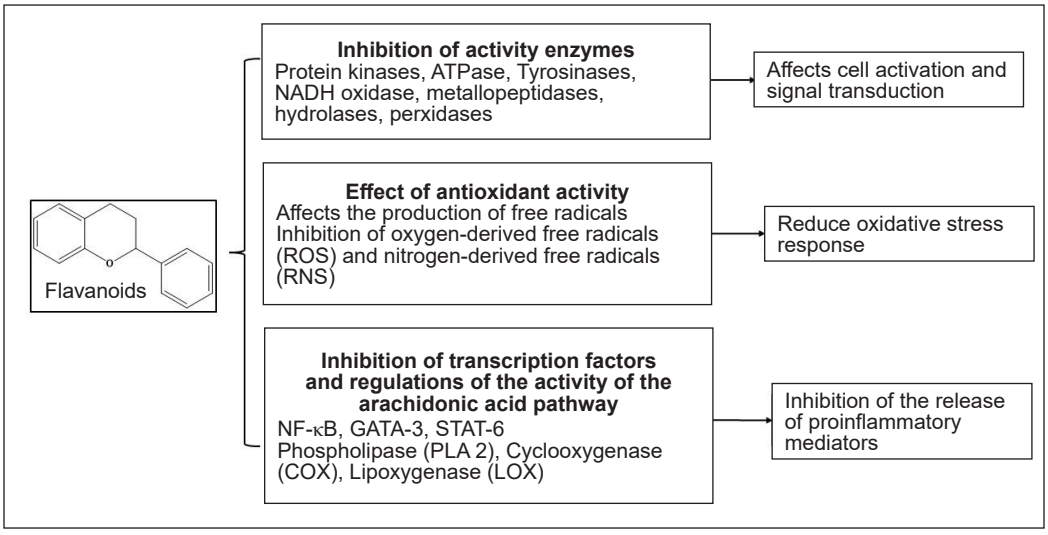

Figure 5. The anti-inflammatory effects of flavonoids

Other Activities

S. grosvenorii-flavonoids have antioxidant, antibacterial and hypoglycemic biological activities that protect the cardiovascular system and relieve fatigue (Zhou, 2022). In addition, some studies have shown that flavonoids in *S. grosvenorii* promote blood circulation and remove blood stasis. It has a protective effect on thrombosis, reduces TC and TG contents in hypercholesterolemic mice, increases HDL-C levels, and prolongs coagulation time in mice.

In summary, there have been many studies on the activity of flavonoids in the past decade, but most of their themes have focused on the antioxidant activity of flavonoids. The ability of flavonoids to act as active agents in vitro has been a hot research topic, and many structure-activity relationships for activity have been established. However, few studies have been conducted on the efficacy of flavonoids in vivo and the mechanisms underlying the distinct types of activity. In order to further develop and utilize the active value of flavonoids, a large number of additional research initiatives are necessary.

CONCLUSION AND FUTURE PERSPECTIVES

This review provides pertinent opinions and ideas for its future development by summarizing the extraction procedure, major constituents, related structures, and biological activities of *S. grosvenorii*-flavonoids. Previous studies have demonstrated that *S. grosvenorii* has tremendous potential as a food additive and medication. Due to their wide variety of biological activities, its various extracts have also been shown to have tremendous application potential. Although mogrosides are believed to be the primary active ingredients in *S. grosvenorii*, other active ingredients contribute to the organism's

functionality. *S. grosvenorii*-flavonoids are an essential component of the plant for which research, development, and utilization are indispensable.

Presently, there are few studies on *S. grosvenorii*-flavonoids, with the majority of these studies focusing on the extraction procedure and a small quantity of activity research. Given the current problems and deficiencies in *S. grosvenorii*-flavonoids research, we have proposed a new direction for future research: (1) in order to further understand the characteristics of *S. grosvenorii* and its extracts, it is necessary to explore and discover more biological activities, (2) in order to better develop and apply the biological activity of *S. grosvenorii*, the mechanisms of its activity should be further explored, (3) based on in vitro activity studies, different levels of activity studies were comprehensively carried out, including *in vivo*, *in ovo,* and (4) make full use of its activity and apply it in related fields.

In conclusion, if fully developed and utilized, *S. grosvenorii's* active compounds will be of immeasurable value for future research. The active components from *S. grosvenorii* still need to be developed further, and more research needs to be done on the individual components' active properties so that new applications can be developed.

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REFERENCES

Abdel-Hamid, M., Romeih, E., Huang, Z., Enomoto, T., Huang, L., & Li, L. (2020). Bioactive properties of probiotic set-yogurt supplemented with *Siraitia grosvenorii* fruit extract. *Food Chemistry, 303*, Article 125400. https://doi.org/10.1016/j.foodchem.2019.125400

Adamczak, A., Ożarowski, M., & Karpiński, T. M. (2019). Antibacterial activity of some flavonoids and organic acids widely distributed in plants. *Journal of Clinical Medicine, 9*(1), Article 109. https://doi.org/10.3390/jcm9010109

Akter, M., Parvin, M. S., Hasan, M. M., Rahman, M. A. A., & Islam, M. E. (2022). Anti-tumor and antioxidant activity of kaempferol-3-O-alpha-L-rhamnoside (Afzelin) isolated from *Pithecellobium dulce* leaves. *BMC Complementary Medicine and Therapies, 22*(1), Article 169. https://doi.org/10.1186/s12906-022-03633-x

Alkhalidy, H., Moore, W., Wang, A., Luo, J., McMillan, R. P., Wang, Y., Zhen, W., Hulver, M. W., & Liu, D. (2018). Kaempferol ameliorates hyperglycemia through suppressing hepatic gluconeogenesis and enhancing hepatic insulin sensitivity in diet-induced obese mice. *The Journal of Nutritional Biochemistry, 58*, 90-101. https://doi.org/10.1016/j.jnutbio.2018.04.014

Alkhalidy, H., Moore, W., Zhang, Y., McMillan, R., Wang, A., Ali, M., Suh, K.S., Zhen, W., Cheng, Z., Jia, Z., & Hulver, M. (2015). Small molecule kaempferol promotes insulin sensitivity and preserved pancreatic

β-cell mass in middle-aged obese diabetic mice. *Journal of Diabetes Research, 2015*, 1-14. https://doi.org/10.1155/2015/532984

Azfaralariff, A., Farahfaiqah, F., Shahid, M., Sanusi, S. A., Law, D., Isa, A. R.M., Muhamad, M., Tsui, T. T., & Fazry, S. (2022). *Marantodes pumilum*: Systematic computational approach to identify their therapeutic potential and effectiveness. *Journal of Ethnopharmacology, 283*, Article 114751. https://doi.org/10.1016/j.jep.2021.114751

Barreca, M. M., Alessandro, R., & Corrado, C. (2023). Effects of flavonoids on cancer, cardiovascular and neurodegenerative diseases: Role of NF-κB signaling pathway. *International Journal of Molecular Sciences, 24*(11), Article 9236. https://doi.org/10.3390/ijms24119236

Beg, M. A., Shivangi, Afzal, O., Akhtar, M. S., Altamimi, A. S., Hussain, A., Imam, M. A., Ahmad, M. N., Chopra, S., & Athar, F. (2022). Potential efficacy of β-Amyrin targeting mycobacterial universal stress protein by *in vitro* and *in silico* approach. *Molecules, 27*(14), Article 4581. https://doi.org/10.3390/molecules27144581

Bian, Y., Lei, J., Zhong, J., Wang, B., Wan, Y., Li, J., Liao, C., He, Y., Liu, Z., Ito, K., & Zhang, B. (2022). Kaempferol reduces obesity, prevents intestinal inflammation, and modulates gut microbiota in high-fat diet mice. *The Journal of Nutritional Biochemistry, 99*, Article 108840. https://doi.org/10.1016/j.jnutbio.2021.108840

Bibbins-Domingo, K. (2016). Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: US preventive services task force recommendation statement. *Annals of Internal Medicine*, *164*(12), 836-845. https://doi.org/10.7326/M16-0577

Cai Shi, D., Long, C., Vardeman, E., Kennelly, E. J., Lawton, M. A., & Di, R. (2023). Potential anti-alzheimer properties of mogrosides in vitamin B12-deficient caenorhabditis elegans. *Molecules, 28*(4), Article 1826. https://doi.org/10.3390/molecules28041826

Chaturvedula, V. S. P., & Prakash, I. (2013). Isolation and structure elucidation of daidzein and genistein from *Siraitia grosvenorii*. *Asian Journal of Pharmaceutical Research and Development, 1*(1), 67-72.

Chen, Y., Zhang, L., Li, Z., Wu, Z., Lin, X., Li, N., Shen, R., Wei, G., Yu, N., Gong, F., & Ji, G. (2022). Mogrol attenuates osteoclast formation and bone resorption by inhibiting the TRAF6/MAPK/NF-κB signaling pathway *in vitro* and protects against osteoporosis in postmenopausal mice. *Frontiers in Pharmacology, 13,* Article 803880. https://doi.org/10.3389/fphar.2022.803880

Cheun-Arom, T., & Sritularak, B. (2023). *In vitro* antidiabetic and advanced glycation end products inhibitory activity of methanol extracts of various dendrobium species. *Journal of Applied Pharmaceutical Science, 13*(6), 100-107. https://doi.org/10.7324/JAPS.2023.75102

Čižmárová, B., Hubková, B., Tomečková, V., & Birková, A. (2023). Flavonoids as promising natural compounds in the prevention and treatment of selected skin diseases. *International Journal of Molecular Sciences, 24*(7), Article 6324. https://doi.org/10.3390/ijms24076324

Dahlén, A. D., Dashi, G., Maslov, I., Attwood, M. M., Jonsson, J., Trukhan, V., & Schiöth, H. B. (2022). Trends in antidiabetic drug discovery: FDA approved drugs, new drugs in clinical trials and global sales. *Frontiers in Pharmacology, 12*, Article 807548. https://doi.org/10.3389/fphar.2021.807548

Dhanya, R., Arya, A. D., Nisha, P., & Jayamurthy, P. (2017). Quercetin, a lead compound against type 2 diabetes ameliorates glucose uptake via AMPK pathway in skeletal muscle cell line. *Frontiers in Pharmacology, 8*, Article 336. https://doi.org/10.3389/fphar.2017.00336

Duan, J., Zhu, D., Zheng, X., Ju, Y., Wang, F., Sun, Y., & Fan, B. (2023). *Siraitia grosvenorii (Swingle) C. Jeffrey*: Research progress of its active components, pharmacological effects, and extraction methods. *Foods, 12*(7), Article 1373. https://doi.org/10.3390/foods12071373

Eid, H. M., & Haddad, P. S. (2017). The antidiabetic potential of quercetin: underlying mechanisms. *Current Medicinal Chemistry, 24*(4), 355-364. https://doi.org/10.2174/0929867323666160909153707

Fang, C., Wang, Q., Liu, X., & Xu, G. (2017). Metabolic profiling analysis of *Siraitia grosvenorii* revealed different characteristics of green fruit and saccharified yellow fruit. *Journal of Pharmaceutical and Biomedical Analysis, 145*, 158-168. https://doi.org/10.1016/j.jpba.2017.06.046

Gong, P., Guo, Y., Chen, X., Cui, D., Wang, M., Yang, W., & Chen, F. (2022). Structural characteristics, antioxidant and hypoglycemic activities of polysaccharide from *Siraitia grosvenorii*. *Molecules,* 27(13), Article 4192. https://doi.org/10.3390/molecules27134192

Gong, X., Chen, N., Ren, K., Jia, J., Wei, K., Zhang, L., Lv, Y., Wang, J. and Li, M. (2019). The fruits of *Siraitia grosvenorii:* A review of a Chinese food-medicine. *Frontiers in Pharmacology, 10*, Article 1400. https://doi.org/10.3389/fphar.2019.01400

Huang, W., Wang, Y., Tian, W., Cui, X., Tu, P., Li, J., Shi, S., & Liu, X. (2022). Biosynthesis investigations of terpenoid, alkaloid, and flavonoid antimicrobial agents derived from medicinal plants. *Antibiotics, 11*(10), Article 1380. https://doi.org/10.3390/antibiotics11101380

Ibrahim, N. N. A., Wan Mustapha, W. A., Sofian-Seng, N. S., Lim, S. J., Razali, N. S. M., Teh, A. H., & Mediani, A. (2023). A comprehensive review with future prospects on the medicinal properties and biological activities of *Curcuma caesia* Roxb. *Evidence-Based Complementary and Alternative Medicine, 2023*, Article 7006565. https://doi.org/10.1155/2023/7006565

Irfan, M., Almotiri, A., & AlZeyadi, Z. A. (2022). Antimicrobial resistance and its drivers - A review. *Antibiotics, 11*(10), Article 1362. https://doi.org/10.3390/antibiotics11101362

Janibekov, A. A., Youssef, F. S., Ashour, M. L., & Mamadalieva, N. Z. (2018). New flavonoid glycosides from two *Astragalus* species (*Fabaceae*) and validation of their antihyperglycaemic activity using molecular modelling and *in vitro* studies. *Industrial Crops and Products, 118*, 142-148. https://doi.org/10.1016/j.indcrop.2018.03.034

Ju, P., Ding, W., Chen, J., Cheng, Y., Yang, B., Huang, L., Zhou, Q., Zhu, C., Li, X., Wang, M., & Chen, J. (2020). The protective effects of Mogroside V and its metabolite 11-oxo-mogrol of intestinal microbiota against MK801-induced neuronal damages. *Psychopharmacology, 237*, 1011-1026. https://doi.org/10.1007/s00213-019-05431-9

Kaur, B., & Singh, P. (2022). Inflammation: Biochemistry, cellular targets, anti-inflammatory agents and challenges with special emphasis on cyclooxygenase-2. *Bioorganic Chemistry*, *121*, 105663. https://doi.org/10.1016/j.bioorg.2022.105663

Keylani, K., Mojeni, F. A., Khalaji, A., Rasouli, A., Aminzade, D., Karimi, M. A., Sanaye, P. M., Khajevand, N., Nemayandeh, N., Poudineh, M., & Deravi, N. (2023). Endoplasmic reticulum as a target in cardiovascular

diseases: Is there a role for flavonoids? *Frontiers in Pharmacology, 13*, Article 1027633. https://doi.org/10.3389/fphar.2022.1027633

Khuntia, A., Martorell, M., Ilango, K., Bungau, S. G., Radu, A. F., Behl, T., & Sharifi-Rad, J. (2022). Theoretical evaluation of Cleome species' bioactive compounds and therapeutic potential: A literature review. *Biomedicine & Pharmacotherapy, 151*, Article 113161. https://doi.org/10.1016/j.biopha.2022.113161

Kropp, M., Golubnitschaja, O., Mazurakova, A., Koklesova, L., Sargheini, N., Vo, T. T. K. S., De Clerck, E., Polivka J. J., Potuznik, P., Polivka, J., Stetkarova, I., Kubatka, P., & Thumann, G. (2023). Diabetic retinopathy as the leading cause of blindness and early predictor of cascading complications - Risks and mitigation. *EPMA Journal, 14*, 21-42. https://doi.org/10.1007/s13167-023-00314-8

Li, D., Jiang, C., Mei, G., Zhao, Y., Chen, L., Liu, J., Tang, Y., Gao, C., & Yao, P. (2020). Quercetin alleviates ferroptosis of pancreatic β cells in type 2 diabetes. *Nutrients, 12*(10), Article 2954. https://doi.org/10.3390/nu12102954

Li, H., Li, R., Jiang, W., & Zhou, L. (2022). Research progress of pharmacological effects of *Siraitia grosvenorii* extract. *Journal of Pharmacy and Pharmacology, 74*(7), 953-960. https://doi.org/10.1093/jpp/rgab150

Li, H., Liu, L., Chen, H. Y., Yan, X., Li, R. L., Lan, J., Xue, K.Y., Li, X., Zhuo, C.L., Lin, L., & Zhou, L. (2022). Mogrol suppresses lung cancer cell growth by activating AMPK-dependent autophagic death and inducing *p53-dependent* cell cycle arrest and apoptosis. *Toxicology and Applied Pharmacology, 444*, Article 116037. https://doi.org/10.1016/j.taap.2022.116037

Li, X., Xu, L. Y., Cui, Y. Q., Pang, M. X., Wang, F., & Qi, J. H. (2018). Anti-bacteria effect of active ingredients of *Siraitia grosvenorii* on the spoilage bacteria isolated from sauced pork head meat. *Conference Series: Materials Science and Engineering, 292*, Article 012012. https://doi.org/10.1088/1757-899X/292/1/012012

Liu, H., Du, Y., Liu, L. L., Liu, Q. S., Mao, H., & Cheng, Y. (2023). Anti-depression-like effect of Mogroside V is related to the inhibition of inflammatory and oxidative stress pathways. *European Journal of Pharmacology, 955,* Article 175828. https://doi.org/10.1016/j.ejphar.2023.175828

Liu, W., Cui, X., Zhong, Y., Ma, R., Liu, B., & Xia, Y. (2023). Phenolic metabolites as therapeutic in inflammation and neoplasms: molecular pathways explaining their efficacy. *Pharmacological Research, 193*, Article 106812. https://doi.org/10.1016/j.phrs.2023.106812

Liu, X., Zhang, J., Li, Y., Sun, L., Xiao, Y., Gao, W., & Zhang, Z. (2019). Mogroside derivatives exert hypoglycemics effects by decreasing blood glucose level in HepG2 cells and alleviates insulin resistance in T2DM rats. *Journal of Functional Foods, 63*, Article 103566. https://doi.org/10.1016/j.jff.2019.103566

Liu, Z., Zhu, X., Mohsin, A., Yin, Z., Zhuang, Y., Zhou, B., Du, L., Yin, X., Liu, N., Wang, Z., & Guo, M. (2022). Embryogenic callus induction, cell suspension culture, and spectrum-effect relationship between antioxidant activity and polyphenols composition of *Siraitia grosvenorii* cultured cells. *Industrial Crops and Products, 176*, Article 114380. https://doi.org/10.1016/j.indcrop.2021.114380

Lu, F., Sun, J., Jiang, X., Song, J., Yan, X., Teng, Q., & Li, D. (2023). Identification and isolation of α-glucosidase inhibitors from *Siraitia grosvenorii* roots using bio-affinity ultrafiltration and comprehensive chromatography. *International Journal of Molecular Sciences, 24*(12), Article 10178. https://doi.org/10.3390/ijms241210178

Lü, W., Ren, G., Shimizu, K., Li, R., & Zhang, C. (2024). Mogroside IIE, an *in vivo* metabolite of sweet agent, alleviates acute lung injury via Pla2g2a-EGFR inhibition. *Food Science and Human Wellness, 13*(1), 299-312. https://doi.org/10.26599/FSHW.2022.9250025

Lu, Y., Zhu, S., He, Y., Mo, C., Wu, C., Zhang, R., Zheng, X., & Tang, Q. (2020). Systematic characterization of flavonoids from *Siraitia grosvenorii* leaf extract using an integrated strategy of high-speed counter-current chromatography combined with ultra-highperformance liquid chromatography and electrospray ionization quadrupole time-of-flight mass spectrometry. *Journal of Separation Science, 43*(5), 852-864. https://doi.org/10.1002/jssc.201900789

Luo, H., Peng, C., Xu, X., Peng, Y., Shi, F., Li, Q., Dong, J., & Chen, M. (2022). The protective effects of mogroside V against neuronal damages by attenuating mitochondrial dysfunction via upregulating Sirtuin3. *Molecular Neurobiology, 59*(4), 2068-2084. https://doi.org/10.1007/s12035-021-02689-z

Mitra, S., Lami, M. S., Uddin, T. M., Das, R., Islam, F., Anjum, J., Hossain, M.J., & Emran, T. B. (2022). Prospective multifunctional roles and pharmacological potential of dietary flavonoid narirutin. *Biomedicine & Pharmacotherapy, 150*, Article 112932. https://doi.org/10.1016/j.biopha.2022.112932

Mo, L., & Li, D. (2009). Antioxidant activity of flavonol glycosides of *Siraitia grosvenorii* flower. *Modern Food Science and Technology, 25*(5), 484-486.

Moudaka, T. E., Murugan, P., Abdul Rahman, M. B., & Tejo, B. A. (2023). Discovery of mycobacterium tuberculosis CYP121 new inhibitor via structure-based drug repurposing. *Pertanika Journal of Science & Technology, 31*(3), 1503-1521. https://doi.org/10.47836/pjst.31.3.21

Najm, A. A., Azfaralarriff, A., Dyari, H. R. E., Alwi, S. S. S., Khalili, N., Othman, B. A., Law. D., Shahid, M., & Fazry, S. (2022). A systematic review of antimicrobial peptides from fish with anticancer properties. *Pertanika Journal of Science & Technology*, *30*(2), 1171-1196. https://doi.org/10.47836/pjst.30.2.18

Ooi, T. C., Ibrahim, F. W., Ahmad, S., Chan, K. M., Leong, L. M., Mohammad, N., & Rajab, N. F. (2021). Antimutagenic, cytoprotective and antioxidant properties of ficus deltoidea aqueous extract *in vitro*. *Molecules, 26*(11), Article 3287. https://doi.org/10.3390/molecules26113287

Pal, R., Kumar, L., Anand, S., & Bharadvaja, N. (2023). Role of natural flavonoid products in managing osteoarthritis. *Revista Brasileira de Farmacognosia, 33*, 663-675. https://doi.org/10.1007/s43450-023-00387-6

Pan, Y., Wei, L., Zhu, Z., Liang, Y., Huang, C., Wang, H., & Wang, K. (2012). Processing of *Siraitia grosvenorii*' leaves: Extraction of antioxidant substances. *Biomass and Bioenergy, 36*, 419-426. https://doi.org/10.1016/j.biombioe.2011.11.011

Pandey, A. K., & Chauhan, O. P. (2019). Monk fruit (*Siraitia grosvenorii*) - Health aspects and food applications. *Pantnagar Journal of Research, 17*(3), 191-198.

Pasala, P. K., Shaik, R. A., Rudrapal, M., Khan, J., Alaidarous, M. A., Khairnar, S. J., Bendale, A. R., Naphade, V. D., Sahoo, R. K., Zothantluanga, J. H., & Walode, S. G. (2022). Cerebroprotective effect of Aloe Emodin: In silico and *in vivo* studies. *Saudi Journal of Biological Sciences, 29*(2), 998-1005. https://doi.org/10.1016/j.sjbs.2021.09.077

Qing, Z. X., Zhao, H., Tang, Q., Mo, C. M., Huang, P., Cheng, P., Yang, P., Yang, X. Y., Liu, X. B., Zheng, Y. J., & Zeng, J. G. (2017). Systematic identification of flavonols, flavonol glycosides, triterpene and siraitic

acid glycosides from *Siraitia grosvenorii* using high-performance liquid chromatography/quadrupole-time-of-flight mass spectrometry combined with a screening strategy. *Journal of Pharmaceutical and Biomedical Analysis, 138*, 240-248. https://doi.org/10.1016/j.jpba.2017.01.059

Rao, R., Yang, R. J., Deng, Y. Y., He, X. Y., Ye, X. C., & Liu, Y. W. (2012). Determination of total flavonoids in *Siraitia grosvenorii* swingle fruit extract and vine leaf extract. *China Pharmacist, 15*, 7-9.

Razak, A. M., Zakaria, S. N. A., Sani, N. F. A., Rani, N. A., Hakimi, N. H., Said, M. M., Jen, K. T., Han, K. G., & Makpol, S. (2023). A subcritical water extract of soil grown Zingiber officinale Roscoe: Comparative analysis of antioxidant and anti-inflammatory effects and evaluation of bioactive metabolites. *Frontiers in Pharmacology, 14*, Article 1006265. https://doi.org/10.3389/fphar.2023.1006265

Septembre-Malaterre, A., Boumendjel, A., Seteyen, A. L. S., Boina, C., Gasque, P., Guiraud, P., & Sélambarom, J. (2022). Focus on the high therapeutic potentials of quercetin and its derivatives. *Phytomedicine Plus, 2*(1), Article 100220. https://doi.org/10.1016/j.phyplu.2022.100220

Sethupathi, P., Matetić, A., Bang, V., Myint, P. K., Rendon, I., Bagur, R., Diaz-Arocutipa, C., Ricalde, A., & Mamas, M. A. (2023). Association of diabetes mellitus and its types with in-hospital management and outcomes of patients with acute myocardial infarction. *Cardiovascular Revascularization Medicine, 52*, 16-22 https://doi.org/10.1016/j.carrev.2023.02.008

Shahid, M., Law, D., Azfaralariff, A., Mackeen, M. M., Chong, T. F., & Fazry, S. (2022). Phytochemicals and biological activities of *Garcinia atroviridis*: A critical review. *Toxics, 10*(11), Article 656. https://doi.org/10.3390/toxics10110656

Shamsudin, N. F., Ahmed, Q. U., Mahmood, S., Shah, S. A. A., Khatib, A., Mukhtar, S., Alsharif, M.A., Parveen, H., & Zakaria, Z. A. (2022). Antibacterial effects of flavonoids and their structure-activity relationship study: A comparative interpretation. *Molecules, 27*(4), Article 1149. https://doi.org/10.3390/molecules27041149

Sharma, D., Tekade, R. K., & Kalia, K. (2020). Kaempferol in ameliorating diabetes-induced fibrosis and renal damage: An *in vitro* and *in vivo* study in diabetic nephropathy mice model. *Phytomedicine, 76*, Article 153235. https://doi.org/10.1016/j.phymed.2020.153235

Shen, J., Shen, D., Tang, Q., Li, Z., Jin, X., & Li, C. (2022). Mogroside V exerts anti-inflammatory effects on fine particulate matter-induced inflammation in porcine alveolar macrophages. *Toxicology in Vitro, 80*, Article 105326. https://doi.org/10.1016/j.tiv.2022.105326

Shen, N., Wang, T., Gan, Q., Liu, S., Wang, L., & Jin, B. (2022). Plant flavonoids: Classification, distribution, biosynthesis, and antioxidant activity. *Food Chemistry, 383*, Article 132531. https://doi.org/10.1016/j.foodchem.2022.132531

Singh, A., Kukreti, R., Saso, L., & Kukreti, S. (2022). Mechanistic insight into oxidative stress-triggered signaling pathways and type 2 diabetes. *Molecules, 27*(3), Article 950. https://doi.org/10.3390/molecules27030950

Song, J. R., Li, N., Wei, Y. L., Lu, F. L., & Li, D. P. (2022). Design and synthesis of mogrol derivatives modified on a ring with anti-inflammatory and anti-proliferative activities. *Bioorganic & Medicinal Chemistry Letters, 74*, Article 128924. https://doi.org/10.1016/j.bmcl.2022.128924

Su, M., Li, Z., Zhou, S., Zhang, H., Xiao, Y., Li, W., Shang, H., & Li, J. (2023). Kaempferitrin, a major compound from ethanol extract of *Chenopodium ambrosioides*, exerts antitumour and hepatoprotective effects in the mice model of human liver cancer xenografts. *Journal of Pharmacy and Pharmacology, 75*(8), 1066-1075. https://doi.org/10.1093/jpp/rgad046

Sung, Y. Y., Yuk, H. J., Yang, W. K., Kim, S. H., & Kim, D. S. (2020). *Siraitia grosvenorii* residual extract attenuates atopic dermatitis by regulating immune dysfunction and skin barrier abnormality. *Nutrients, 12*(12), Article 3638. https://doi.org/10.3390/nu12123638

Suriyaprom, S., Srisai, P., Intachaisri, V., Kaewkod, T., Pekkoh, J., Desvaux, M., & Tragoolpua, Y. (2023). Antioxidant and anti-inflammatory activity on LPS-stimulated RAW 264.7 macrophage cells of white mulberry (*Morus alba* L.) leaf extracts. *Molecules, 28*(11), Article 4395. https://doi.org/10.3390/molecules28114395

Thakur, K., Partap, M., Kumar, P., Sharma, R., & Warghat, A. R. (2022). Understandings of bioactive composition, molecular regulation, and biotechnological interventions in the development and usage of specialized metabolites as health-promoting substances in *Siraitia grosvenorii* (Swingle) C. Jeffrey. *Journal of Food Composition and Analysis, 116*, Article 105070. https://doi.org/10.1016/j.jfca.2022.105070

Wang, M., Xing, S., Luu, T., Fan, M., & Li, X. (2015). The gastrointestinal tract metabolism and pharmacological activities of *grosvenorine*, a major and characteristic flavonoid in the fruits of *Siraitia grosvenorii*. *Chemistry & Biodiversity, 12*(11), 1652-1664. https://doi.org/10.1002/cbdv.201400397

Wang, Y., Li, H. B., Bai, X. F., Zhang, M., Li, X. M. (2006). Study on enzyme-solvent extraction process for flavonoid from *Momordica grosvenorii*. *Food Science and Technology, 31*, 125-127.

Wu, J., Jian, Y., Wang, H., Huang, H., Gong, L., Liu, G., Yang, Y., & Wang, W. (2022). A review of the phytochemistry and pharmacology of the fruit of *Siraitia grosvenorii* (Swingle): A traditional Chinese medicinal food. *Molecules, 27*(19), Article 6618. https://doi.org/10.3390/molecules27196618

Wuttisin, N., & Boonsook, W. (2019). Total phenolic, flavonoid contents and antioxidant activity of *Siraitia grosvenorii* fruits extracts. *Food and Applied Bioscience Journal, 7*(3), 131-141.

Xu, H., Xu, M., Yuan, F., & Gao, Y. (2017). Chemical and antioxidant properties of functional compounds extracted from Siraitia grosvenorii by subcritical water. *Acta Alimentaria, 46*(2), 162-171. https://doi.org/10.1556/066.2016.0006

Yanan, S., Bohan, L., Shuaifeng, S., Wendan, T., Ma, Z., & Wei, L. (2023). Inhibition of Mogroside IIIE on isoproterenol-induced myocardial fibrosis through the TLR4/MyD88/NF-κB signaling pathway. *Iranian Journal of Basic Medical Sciences, 26*(1), 114-120.

Yang, L., Zeng, S., Li, Z. H., & Pan, Y. M. (2016). Chemical components of the leaves of *Siraitia grosvenorii*. *Chemistry of Natural Compounds, 52*, 891-892. https://doi.org/10.1007/s10600-016-1805-2

Yang, Z., Wang, H., Qi, G., Chen, G., Cao, C., & Wang, S. (2022). Antimicrobial effects of a compound solution of three medicine food homology plants. *Food Bioscience, 49*, Article 101845. https://doi.org/10.1016/j.fbio.2022.101845

Yedjou, C. G., Grigsby, J., Mbemi, A., Nelson, D., Mildort, B., Latinwo, L., & Tchounwou, P. B. (2023). The management of diabetes mellitus using medicinal plants and vitamins. *International Journal of Molecular Sciences, 24*(10), Article 9085. https://doi.org/10.3390/ijms24109085

Zang, E., Jiang, L., Cui, H., Li, X., Yan, Y., Liu, Q., Chen, Z., & Li, M. (2022). Only plant-based food additives: An overview on application, safety, and key challenges in the food industry. *Food Reviews International, 39*(8), 5132-5163. https://doi.org/10.1080/87559129.2022.2062764

Zhang, C., Rong, D., & Zhang, Z. (2013). 罗汉果花中黄酮的提取及结构表征(Extraction and structural characterization of flavonoids from monk fruit flowers). *Spectroscopy Laboratory, 30*(3), 1389-1394. https://doi.org/10.3969/j.issn.1004-8138.2013.03.080

Zhang, H. Y., Yang, H. H., Zhang, M., Wang, Y. R., Wang, J. R., Jiang, Z. H., & Hu, P. (2013). Comparative analysis of chemical constituents in different parts of Siraitia grosvenorii using UPLC-MS combined with pattern recognition. *Chinese Traditional and Herbal Drugs, 44*(1), 19-23.

Zhang, Y., Zhou, G., Peng, Y., Wang, M., & Li, X. (2020). Anti-hyperglycemic and anti-hyperlipidemic effects of a special fraction of luo han guo extract on obese T2DM rats. *Journal of Ethnopharmacology, 247*, Article 112273. https://doi.org/10.1016/j.jep.2019.112273

Zhang, Z., Li, X., Sang, S., McClements, D. J., Chen, L., Long, J., Jiao, A., Jin, Z., & Qiu, C. (2022). Polyphenols as plant-based nutraceuticals: Health effects, encapsulation, nano-delivery, and application. *Foods, 11*(15), Article 2189. https://doi.org/10.3390/foods11152189

Zhang, Z. R., Sun, G. R., Duan, X. Y., & Jiang, G. Q. (2016) Optimization of ultrasonic-assisted extraction process for total flavonoids from *Siraitia grosvenorii* flower by response surface methodology. *Hubei Agricultural Science, 55*, 1518-1522.

Zhou, H. (2022). Study on the role of nutrients in food to improve the motion state of athletes. *Italian Journal of Food Science, 34*(2), 28-33. https://doi.org/10.15586/ijfs.v34i2.2126

Zhu, Y. M., Pan, L. C., Zhang, L. J., Yin, Y., Zhu, Z. Y., Sun, H. Q., & Liu, C. Y. (2020). Chemical structure and antioxidant activity of a polysaccharide from *Siraitia grosvenorii*. *International Journal of Biological Macromolecules, 165*, 1900-1910. https://doi.org/10.1016/j.ijbiomac.2020.10.127