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Review

Natural Sweeteners: Biosynthesis and Pharmacological

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Abstract: Natural sweeteners have gained attention as promising alternatives to artificial sweeteners and traditional sugars due to their low or zero-calorie content and diverse bioactive properties. This review examines several key natural sweeteners, including steviol glycosides, mogrosides, glycyrrhizin, neohesperidin, and fructooligosaccharides. The biosynthetic pathways of these sweeteners, combined with their health benefits, make them valuable in managing metabolic disorders like diabetes and obesity. This article also discusses their potential applications in the food, pharmaceutical, and nutraceutical industries, highlighting their role in promoting healthier dietary practices. Further research is needed to optimize their production and fully assess their long-term health impacts, which will be essential for unlocking their therapeutic potential.

Keywords: sweetener, steviol glycoside, mogroside, glycyrrhizin, neohesperidin, fructooligosaccharides

1. Introduction

In recent years, natural sweeteners have garnered significant attention due to their potential health benefits and wide applications in the food and pharmaceutical industries. Unlike traditional artificial sweeteners and high-calorie sugars, natural sweeteners not only provide healthier low- or zero-calorie alternatives but also exhibit a range of bioactive properties, including antioxidant, anti-inflammatory, and anti-diabetic effects, which make them particularly advantageous for managing metabolic disorders. Common examples of natural sweeteners include steviol glycosides derived from *Stevia rebaudiana*, mogrosides from *Siraitia grosvenorii* (monk fruit), glycyrrhizin from licorice, neohesperidin, and fructooligosaccharides (Table 1). These sweeteners are extensively utilized in foods and beverages for their sweetness, while also demonstrating significant potential in regulating blood glucose levels, improving metabolic health, and reducing inflammation. As awareness of metabolic diseases such as diabetes and obesity continues to rise, the role of natural sweeteners in promoting a healthier diet is becoming increasingly relevant. This review will explore the biosynthetic pathways and pharmacological activities of these natural sweeteners, highlighting their potential for future health applications.

Table 1. Five common natural sweeteners.

Compound Name	Category	Source	Relative Sweetness to Sucrose
Steviol Glycosides	Glycosides	Stevia leaves (*Stevia rebaudiana*)	30–320 times
Mogrosides	Triterpene Glycosides	Monk fruit (*Siraitia grosvenorii*)	100–250 times
Glycyrrhizin	Triterpene Glycosides	Licorice root (*Glycyrrhiza glabra*)	50 times
Neohesperidin	Flavonoids	Citrus peels	\
Fructooligosaccharides	Oligosaccharides	Natural fruits, vegetables, and plant fibers	0.3–0.5 times

2. Steviol Glycosides

Steviol glycosides (SGs) are natural sweeteners derived from the leaves of the South American plant *Stevia rebaudiana*. They are widely utilized in food and beverages as low- or zero-calorie sweeteners. In addition to *Stevia rebaudiana*, related species such as *S. phlebophylla* and the Rosaceae plant *Rubus chingii* also contain these compounds. SGs are reported to be 30 to 320 times sweeter than sucrose, and they are not metabolized by the human body, meaning they do not trigger a glycemic response. This property makes them suitable for individuals with diabetes or those managing blood sugar levels. However, the taste profile of SGs varies depending on the specific glycoside. For instance, rebaudioside M is recognized for its favorable taste profile compared to stevioside and rebaudioside A, which may sometimes exhibit a bitter aftertaste. The primary SGs found in Stevia leaves include stevioside (5–10%), dulcoside A (0.5–1%), rebaudioside A (2–4%), and rebaudioside C (1–2%). Commercially available SG mixtures typically consist of approximately 80% stevioside, 8% rebaudioside A, and 0.6% rebaudioside C. The first isolation of stevioside and rebaudioside A was accomplished by French chemists Bridel and Lavielle in 1931 [1]. The Stevia market size is estimated at USD 0.84 billion in 2024, and is expected to reach USD 1.36 billion by 2029, growing at a compound annual growth rate (CAGR) of 10.12% during the forecast period (2024–2029) [2]. Steviol glycosides are considered safe sweeteners. In 2006, following an analysis of several studies on stevia and steviol glycosides in humans and animals, the World Health Organization (WHO) stated that 'stevioside and rebaudioside A are not genotoxic in vitro or in vivo and that the genotoxicity of steviol and some of its oxidative derivatives in vitro is not expressed in vivo [3].

2.1 Biosynthesis

SGs, the primary sweetening compounds in *Stevia rebaudiana*, are diterpenoid glycosides, and their biosynthesis has been extensively studied [4,5]. These glycosides are synthesized via the methylerythritol phosphate (MEP) pathway, which operates independently of the mevalonate (MVA) pathway. This discovery was made using glucose labelling to follow the biosynthetic pathway. The MEP pathway plays a crucial role in forming the diterpenoid glycoside backbone of SGs in *S. rebaudiana* [6,7]. The condensation reaction catalysed by 1-deoxy-d-xylulose 5-phosphate synthase (DXS) is the first step in the MEP pathway [8]. In this reaction, pyruvate and glyceraldehyde 3-phosphate (G3P) are converted to 1-deoxy-D-xylulose 5-phosphate (DXP) under the catalysis of DXS [9]. DXS is the rate-limiting enzyme in the MEP pathway and controls the flux through the pathway [10,11]. DXP is then reduced to MEP by 1-deoxy-D-xylulose 5-phosphate reductoisomerase (DXR). The subsequent steps in the MEP pathway involve the enzymes 4-pyrophosphate 2-C-methyl-D-erythritol synthase (CMS), 4-pyrophosphate 2-C-methyl-D-erythritol kinase (CMK) and 2-C-methyl-D-erythritol 2,4-cyclopyrophosphate synthase (MCS), which, together with (E)-4-hydroxy-3-methylbut-2-enyl pyrophosphate synthase (HDS), catalyse the complex bio-organometallic mechanism that converts MEP to (E)-4-hydroxy-3-methylbut-2-enyl pyrophosphate (HMBPP) [12]. Finally, HMBPP is reduced to isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP) by (E)-4-hydroxy-3-methylbut-2-enyl pyrophosphate reductase (HDR) through a similar mechanism [13]. The interconversion between IPP and DMAPP is facilitated by isopentenyl pyrophosphate isomerase (IDI) [11]. Following the discovery of the diterpenoid properties of steviol, the biosynthesis of the diterpene moiety of stevioside begins with the addition of IPP units to dimethylallyl diphosphate to form geranylgeranyl diphosphate (GGPP) [14]. GGPP is converted to ent-kaurene by copalyl diphosphate synthase (CPPS) and kaurene synthase (KS) through the release of energy, and then produces (-)-kaurene acid ((-)-KA) through the three-step oxidation reaction of kaurene oxidase (KO) [15]. Next, the hydroxylation reaction of ent-KA at C13 under the catalysis of kaurenoic acid 13-hydroxylase (KAH) is the key step to produce SGs [16].

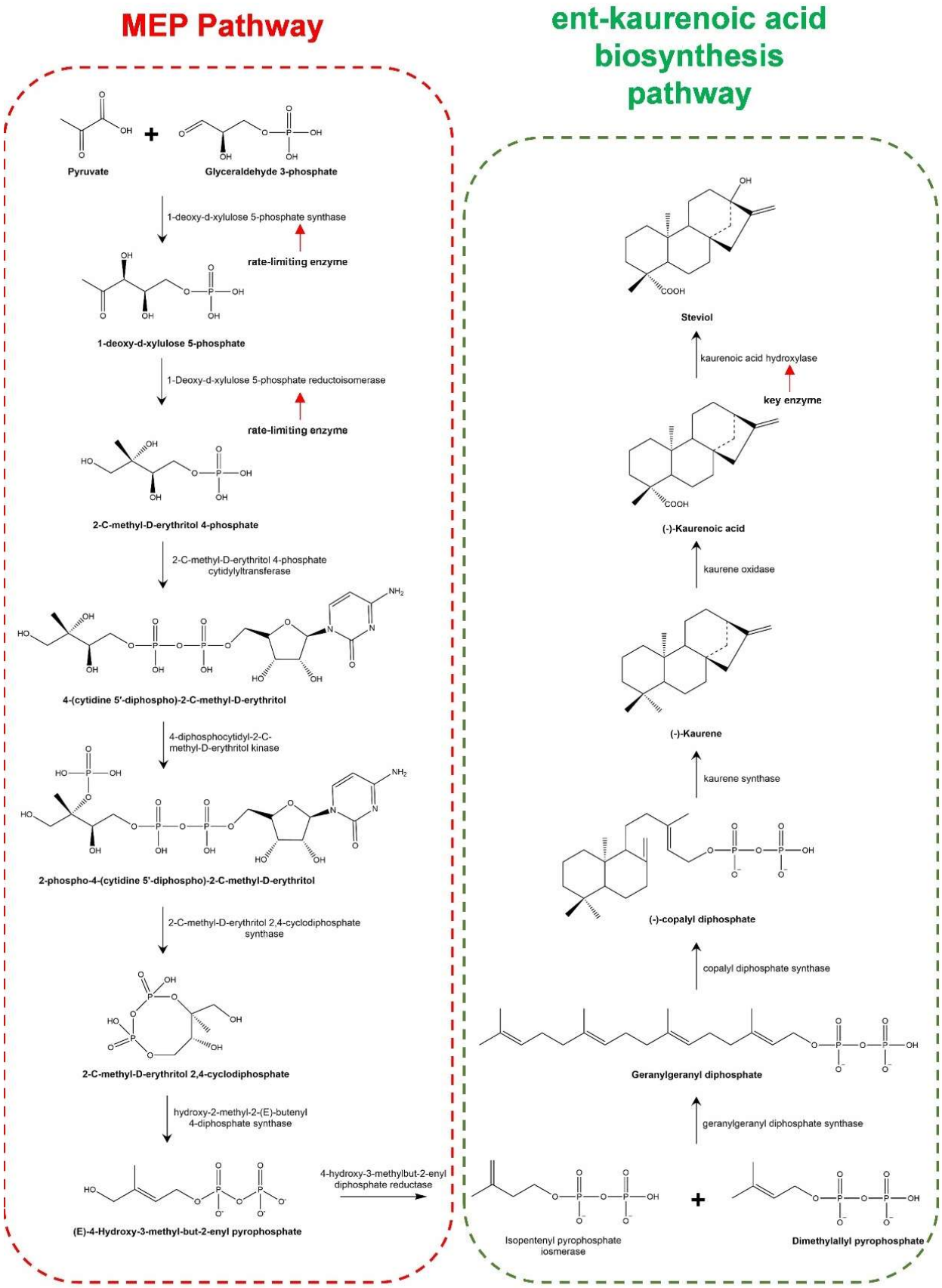

Figure 1. The biosynthesis process of steviol.

2.2 Bioactive

SGs, natural non-caloric sweeteners extracted from *Stevia rebaudiana*, have demonstrated a wide range of physiological activities and are widely used in the food and pharmaceutical industries. Extensive research highlights their potential to promote metabolic health, reduce inflammation, and protect the liver. For example, SGs have been shown to alleviate insulin resistance and obesity-related metabolic disorders by improving glucose tolerance, reducing oxidative stress, and downregulating inflammatory gene expression [17]. In a separate study using high-fat diet-induced and diabetic rat models, SGs effectively regulated lipid metabolism, ameliorated hyperlipidemia, and attenuated associated organ damage [18]. Furthermore, SGs have been observed to improve glucose and lipid metabolism by modulating genes related to these pathways, showing beneficial effects in diabetic rats [19]. Similarly, in adipocyte models, SGs inhibited adipogenesis and lipid accumulation while significantly enhancing insulin sensitivity [20].

The potential metabolic benefits of SGs in humans have also been supported by several studies. A meta-analysis reported a significant reduction in fasting blood glucose levels, particularly in non-diabetic and overweight individuals, although the effect on glycated hemoglobin (HbA1c) was not statistically significant [21]. In addition, the daily consumption of beverages containing SGs did not significantly alter gut microbiota composition, but showed greater suppression of weight gain compared to sucrose consumption [22]. In terms of weight management, one study found that replacing sugar with SGs led to a significant reduction in body weight and waist circumference in overweight and pre-diabetic adults [23].

Derivatives of SGs have also shown remarkable biological activities. For example, Reb M8, synthesized by selective enzymatic glycosylation, not only exhibits enhanced sweetness, but also significantly inhibits tumor necrosis factor-alpha (TNF-α), suggesting potent anti-inflammatory effects [24]. Furthermore, in combination studies, SGs co-administered with L-arginine and trivalent chromium improved insulin sensitivity and reduced blood glucose levels in diabetic rats [25].

SGs have also been shown to have protective effects on the liver. In one study, SGs and their extracts significantly reduced radiation-induced liver damage by reducing inflammatory markers and oxidative stress [26]. Another study showed that the inclusion of SGs and dried stevia leaves improved antioxidant capacity and lipid profiles in rats [27]. In addition, SGs have been found to stimulate the release of GLP-1 via activation of bitter taste receptor signaling pathways, further enhancing their regulatory effects on glucose metabolism [28].

In summary, SGs have broad physiological activities, including benefits in diabetes management, weight control, metabolic regulation, and liver protection, making them promising candidates for various therapeutic and dietary applications.

3. Mogrosides

Mogrosides are triterpenoid glycosides of cucurbitane derivatives, a type of sugar substitute, found in plants such as monk fruit [29]. The total content of mogrosides in monk fruit is 3.8%, with mogroside V being the highest (0.8% to 1.3% by weight) [30]. Some mogrosides are used in traditional Chinese medicine, and some are extracted

and used as sweeteners [29]. Mogroside V extracted from monk fruit is 250 times sweeter than sucrose [29] and is expected to grow at a CAGR of 4.8% from 2023 to 2031 [2]. Unlike sugar, mogroside contributes no calories, making it an attractive alternative for people managing their weight or blood sugar levels. The process of extracting and refining mogroside is relatively complex, and there are costs associated with growing and harvesting the monk fruit (the source of mogroside). Therefore, although it is a zero-calorie, natural sweetener, it is more expensive than synthetic sweeteners such as aspartame or stevia. Mogroside's sweetness is clean and doesn't typically exhibit the bitter aftertaste associated with some other natural sweeteners such as stevia. However, depending on the formulation, it may have a slight aftertaste that some people find less desirable. In addition, Mogroside is heat stable, making it suitable for use in cooking and baking. Toxicity studies have shown that mogrosides are non-toxic and have no mutagenic, genotoxic or other adverse effects [31,32].

3.1 Biosynthesis

The basic structure of mogrosides, the sweet components of *Siraitia grosvenorii* (monk fruit), is a cucurbitane-type triterpenoid saponin. In recent years, the biosynthetic pathway of mogrosides, starting from acetyl-CoA, has been fully elucidated [29,33,34]. This process can be divided into the following key steps: (1) the synthesis of IPP and DMAPP via the MVA pathway; (2) the synthesis of 2,3:22,23-diepoxysqualene; (3) the synthesis of mogrol; (4) the synthesis of mogrosides.

IPP and DMAPP are C5 precursors in terpene biosynthesis and can be synthesised by either the MVA or MEP pathways. In the MVA pathway, two molecules of acetyl-CoA are first condensed to form acetoacetyl-CoA, which is then combined with another molecule of acetyl-CoA under the catalysis of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) synthase (HMGS) to form HMG-CoA. HMG-CoA is reduced to MVA by HMG-CoA reductase (HMGR), and through the sequential catalysis of mevalonate 5-kinase, phosphomevalonate kinase, and mevalonate 5-diphosphate decarboxylase, MVA is converted to IPP. IPP and DMAPP can be interconverted via isomerase activity [35]. In the MEP pathway, G3P is condensed to form DXP. DXP is then reduced to MEP by DXR. MEP is then catalyzed by 2-C-methyl-D-erythritol 4-phosphate cytidylyltransferase (MCT) to produce 4-(cytidine 5′-diphospho)-2-C-methyl-D-erythritol (CD-ME). CD-ME is converted to HMBPP through a series of enzymatic actions, including phosphorylation, cyclization and ring opening. Finally, HMBPP is reduced by 4-hydroxy-3-methylbut-2-enyl diphosphate reductase to form IPP and DMAPP [36].

IPP and DMAPP undergo a head-to-tail condensation catalyzed by geranyl pyrophosphate synthase (GPS) to form geranyl diphosphate (GPP) with a C10 backbone. GPP in turn, condenses with another IPP molecule under the catalysed by farnesyl pyrophosphate synthase (FPS) to form farnesyl diphosphate (FPP), a C15 compound [37]. Squalene synthase (SQS) catalyzes the head-to-tail condensation of two FPP molecules to form squalene, which undergoes two successive epoxidation reactions catalyzed by squalene epoxidase (SE) to form 2,3:22,23- diepoxysqualene.

The synthesis of mogrol begins with the conversion of 2,3:22,23-diepoxysqualene to 24,25-epoxycucurbitadienol, catalyzed by cucurbitadienol

synthase. This intermediate is then converted to cucurbitadienol with hydroxyl groups at the C24 and C25 positions via epoxide hydrolase activity. Finally, mogrol is produced by the hydroxylation of cucurbitadienol at the C11 position by cytochrome P450 (CYP) enzymes [29].

Various UDP-glucosyltransferases (UGTs) add glucose moieties to the C3 and C24 positions of mogrol, and further glucose units are linked via β-1,6 and β-1,2 glycosidic linkages to form various branched structures, resulting in the synthesis of different mogrosides [38].

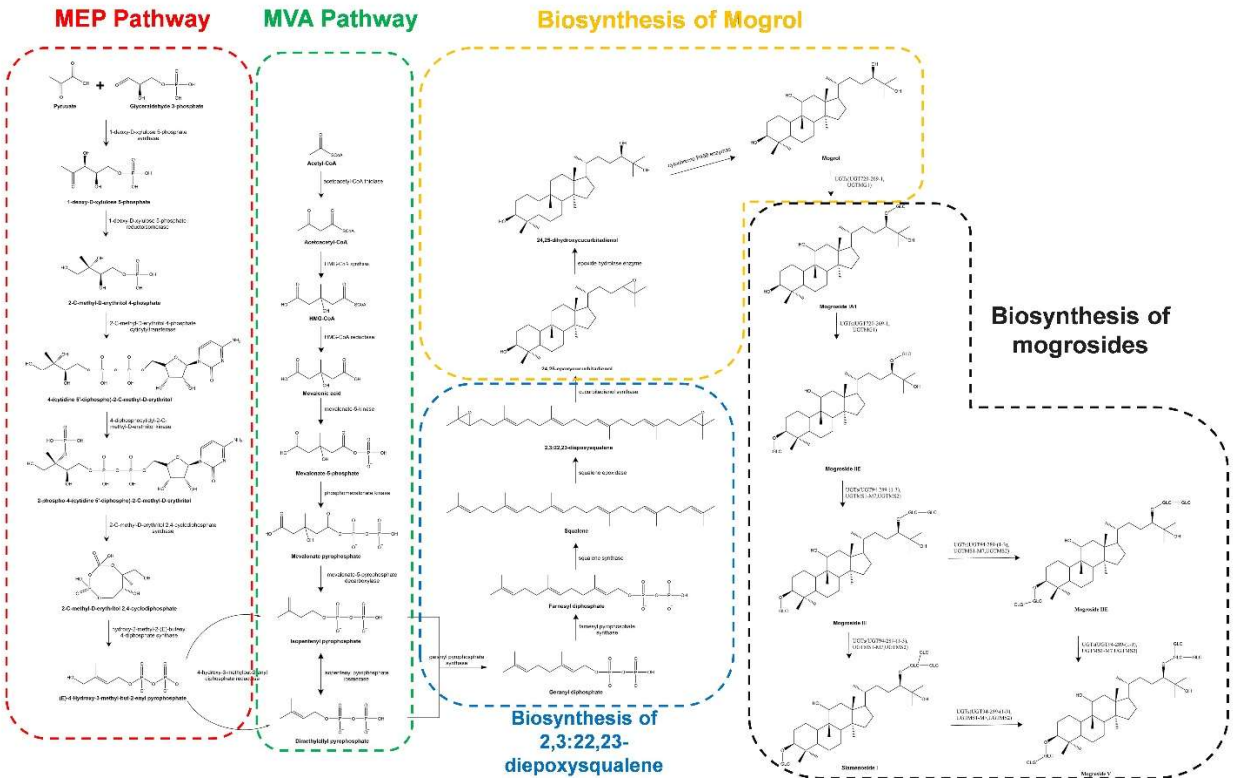

Figure 2. The biosynthesis process of mogrosides. GLC: glucose; UGTs: UDP-glucosyltransferases.

3.2 Bioactive

Mogrosides, particularly Mogroside V, have demonstrated significant therapeutic potential in various biological systems. In studies using obese **Type 2 diabetes** rat models, mogrosides were shown to significantly reduce fasting blood glucose and insulin resistance, while improving lipid profiles, thereby highlighting their role in modulating insulin secretion and activating **5' adenosine monophosphate-activated protein kinase** [39]. In addition, mogrosides positively influenced the gut microbiota in T2DM rats, leading to increased production of short-chain fatty acids, such as butyrate, which are associated with improved gut health and anti-diabetic effects [40].

In addition to its anti-diabetic properties, Mogroside V has shown potent anti-inflammatory activity. In colitis models, Mogroside V inhibited key inflammatory pathways, including MAPK-NF-κB and AMPK-PI3K/Akt/mTOR, suggesting its potential as a therapeutic candidate for the treatment of ulcerative colitis [40]. Similarly, in models of pulmonary inflammation, Mogroside V alleviated asthma-like

symptoms by modulating JAK-STAT and NF-κB signaling pathways, further highlighting its anti-inflammatory potential in respiratory diseases [41]. Furthermore, Mogroside IIE, a metabolite of Mogroside V, was shown to reduce acute lung injury by inhibiting Pla2g2a-EGFR interactions and downregulating the AKT-mTOR signaling pathway, offering potential therapeutic benefits in lung inflammation [42].

Mogroside V also demonstrated potent antioxidant properties. Studies in skin fibroblasts shown that Mogroside V reduced oxidative stress by decreasing reactive oxygen species (ROS) levels and enhancing the activity of antioxidant enzymes such as superoxide dismutase (SOD) and catalase, positioning it as a promising anti-aging agent for skincare applications [43]. Furthermore, its protective effects against hydrogen peroxide-induced oxidative stress in skin fibroblasts support its potential use in anti-aging cosmetic products [43].

In addition to these findings, Mogroside V has demonstrated potential in the treatment of complex diseases beyond diabetes and inflammation. Preclinical in silico studies have identified Mogroside V as a promising therapeutic agent for the treatment of ovarian cancer and COVID-19 by targeting critical molecular mechanisms involved in both diseases [44].

4. Glycyrrhizin

Glycyrrhizin is the main sweetening constituent of the root of *Glycyrrhiza glabra* (licorice). Structurally, it is a saponin. Glycyrrhizin is an extract obtained by macerating the licorice root and boiling it in water [45]. Licorice extract (glycyrrhizin) is sold in the United States as a liquid, paste, or spray-dried powder [45]. It is approved for use in certain amounts as a flavouring and fragrance in processed foods, beverages, confectionery, dietary supplements and spices [45]. It is 30 to 50 times sweeter than sucrose (table sugar) [46]. Despite the beneficial effects of liquorice, toxicity has also been reported with frequent and excessive consumption [47]. Based on in vivo studies in rats and mice, consumption of 15–229 mg/kg/day was suggested to be safe [48]. Continuous high-level exposure to glycyrrhizin is capable of producing hypermineralocorticoid-like effects; however, these effects are reversible upon withdrawal of liquorice and/or glycyrrhizin [48]. Both liquorice and glycyrrhizin have been approved for use in food products by most national and supranational regulatory agencies; however, in addition to the previously recommended dosage, the susceptibility to glycyrrhizin toxicity must be considered as it is directly related to the general health status of the individual [48,49]. The global market for glycyrrhizic acid is expected to grow at a CAGR of 6.8% between 2023 and 2030 [2].

4.1 Biosynthesis

Glycyrrhizin is synthesised by a complex biosynthetic pathway that involves several key enzymatic steps [50]. This pathway begins with the production of isopentenyl diphosphate (IPP), an essential precursor in the biosynthesis of terpenoids.

IPP is produced by a series of enzymatic reactions [51]. Isopentenyl diphosphate isomerase (IPPI) catalyses the isomerisation of IPP to DMAPP. Under the catalysis of farnesyl diphosphate synthase (FPPS), two molecules of IPP and one molecule of DMAPP are sequentially condensed to form FPP [52]. Two molecules of FPP are then

condensed by SQS to form squalene [53]. Squalene is further converted to 2,3-oxidosqualene under the catalysis of squalene synthase [54]. 2,3-oxidosqualene is a crucial branch point in the biosynthesis of glycyrrhizin. Under the action of β-amyrin synthase (β-AS), 2,3-oxidosqualene is converted to β-amyrin [55]. The cytochrome P450 monooxygenases CYP88D6 and CYP72A154 catalyse two consecutive oxidation reactions at the C11 position and three oxidation reactions at the C30 position of β-amyrin, leading to the formation of glycyrrhetinic acid [56,57]. Finally, Glycyrrhiza uralensis UDP-glucosyltransferase 3 sequentially transfers two glucuronide moieties to the C3 position of glycyrrhetinic acid, resulting in the production of glycyrrhizin [58].

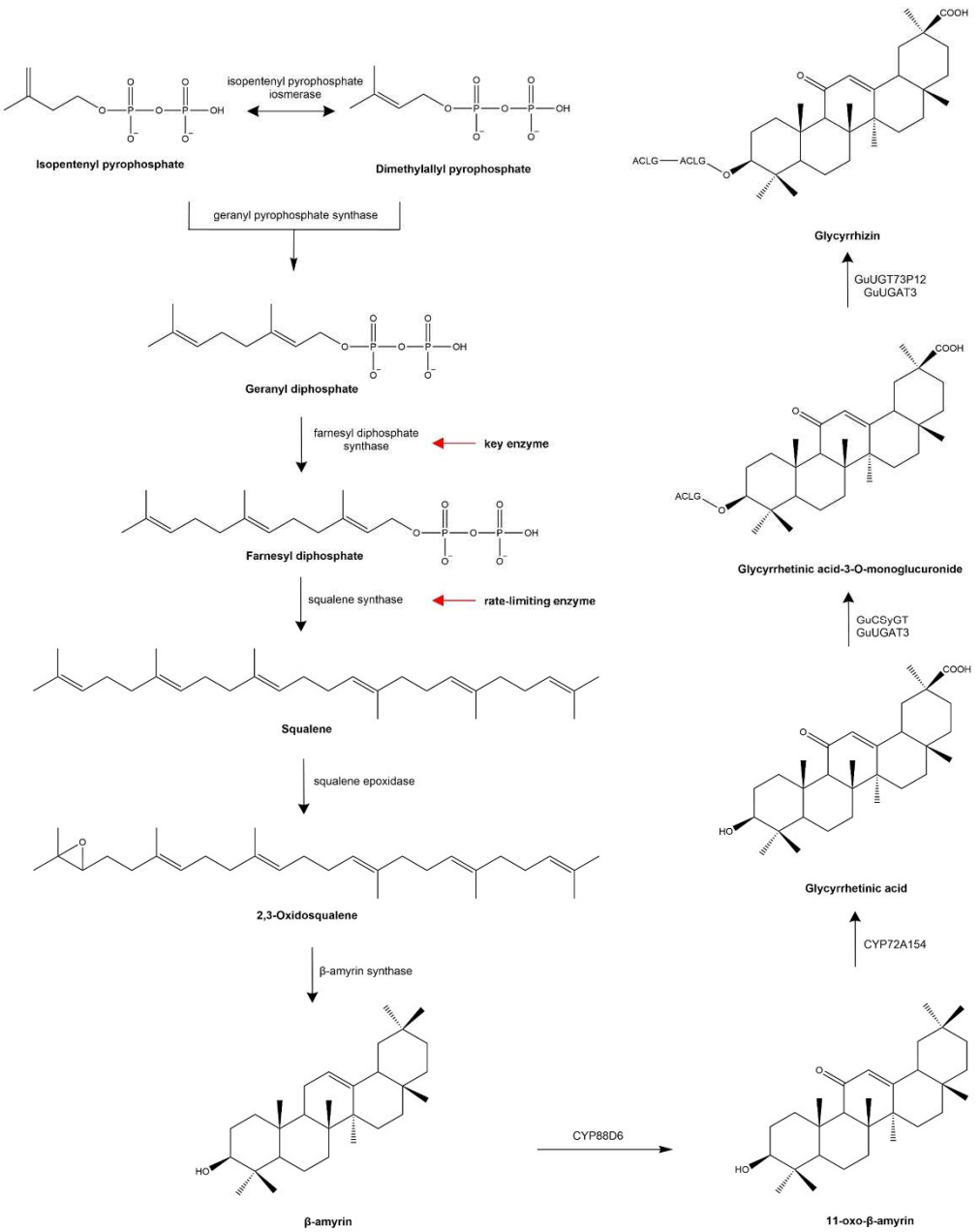

Figure 3. The biosynthesis process of glycyrrhizin. CYP88D6: beta-amyrin 11-oxidase; CYP72A154: 11-oxo-beta-amyrin 30-oxidase; GuUGT3: G. uralensis UDP-glycosyltransferase 3; GuCSyGT: G. uralensis cellulose synthase superfamily-derived glycosyltransferase; GuUGT73P12: G. uralensis UDP-glycosyltransferase 73P12; GLC: glucose.

4.2 Bioactive

Glycyrrhizin and glycyrrhetinic acid, two major bioactive compounds derived from licorice, have demonstrated extensive therapeutic potential in various biomedical fields. Glycyrrhizin is particularly noted for its potent antioxidant properties, which result from its ability to inhibit the formation of reactive oxygen species (ROS) and scavenge free radicals, making it a valuable agent in antioxidant therapies and drug delivery systems [59]. In addition, glycyrrhizin has been shown to possess neuroprotective effects, significantly improving cognitive performance and reducing oxidative damage in animal models of cognitive impairment [60].

Glycyrrhetinic acid, in contrast, has been extensively studied for its potential to enhance bioavailability and anti-inflammatory effects when formulated with solubilisers such as Soluplus®. This formulation approach has been shown to significantly enhance the therapeutic efficacy of glycyrrhetinic acid without significant toxicity [61]. In addition, glycyrrhizin has the ability to form inclusion complexes and micelles, which increase the solubility and bioavailability of poorly soluble drugs, thereby improving their therapeutic efficacy [62].

Both glycyrrhizin and glycyrrhetinic acid have shown potent antiviral properties, especially glycyrrhizin derivatives, which have been found to effectively inhibit the replication of viruses such as SARS-CoV and COVID-19 through interference with viral replication mechanisms and modulation of immune responses [63]. In addition, glycyrrhetinic acid derivatives have demonstrated significant anti-tumor activity, particularly through their function as peroxisome proliferator-activated receptor gamma agonists, which promote apoptosis in cancer cell lines [64].

Glycyrrhizin's ability to form micelles and inclusion complexes not only enhances drug solubility but also potentiates the antioxidant activity of compounds such as carotenoids, making it a promising tool in drug delivery systems aimed at improving the stability and bioavailability of therapeutic agents [65]. This property is also instrumental in enhancing the pharmacological effects of other drugs, including anti-inflammatory and anticancer agents [66]. In addition, chemical modifications of glycyrrhetinic acid have resulted in improved anti-inflammatory efficacy, offering potential benefits in the treatment of inflammatory diseases [67].

In liver-related applications, glycyrrhizin has been shown to offer significant hepatoprotective effects, including reducing liver damage, inhibiting hepatic fibrosis, and enhancing antiviral and anti-inflammatory activities [68]. Furthermore, glycyrrhizin and its derivatives exhibit broad antioxidant activity, protecting against oxidative stress by scavenging free radicals and preventing lipid peroxidation [63]. Its ability to enhance the therapeutic potential of other drugs through complex formation further underscores its utility in multiple therapeutic applications [69].

More importantly, glycyrrhizin has also shown anti-inflammatory activity in vivo. In a meta-analysis evaluating the anti-inflammatory activity and safety of compound glycyrrhizin in the treatment of ulcerative colitis, it was shown that glycyrrhizin

significantly decreased the levels of TNF-α, IL-6, IL-8, and IL-17 and increased the expression of IL-10, which supports the anti-inflammatory effect of glycyrrhizin in the treatment of ulcerative colitis [70]. Glycyrrhizin also showed potential anti-inflammatory activity in inhibiting inflammation in patients with acne and cartilage inflammation in patients with osteoarthritis [71,72].

In conclusion, glycyrrhizin and glycyrrhetinic acid demonstrate a wide range of pharmacological applications, including antioxidant, antiviral, anti-inflammatory, hepatoprotective, and antitumor activities. Their ability to enhance drug solubility and efficacy, coupled with their low toxicity, positions them as promising candidates for future drug development across multiple therapeutic areas.

5. Neohesperidin

Neohesperidin, a semi-natural molecule from bitter orange. Treatment of neohesperidin with hot alkali leads to the opening of heterocyclic rings and the formation of the chalcone form of the flavanone glycoside [73]. Hydrogenation then takes place at the ethylenic double bond of the chalcone to produce the corresponding dihydrochalcones, neohesperidin dihydrochalcone (NHDC), which have an extremely high sweetening potential. Compared to aspartame, NHDC is stable even at high temperatures or under acidic/alkaline conditions, allowing it to remain food safe for up to five years when stored under optimal conditions [73]. Additionally, NHDC shows a synergistic sweetening effect when it is blended with a series of sweeteners [73]. In 2022, the European Food Safety Authority Panel on Food Additives and Flavorings conducted a re-evaluation of NHDC as a food additive, which proposed an acceptable daily intake of 20 mg/kg BW and the bioavailability of NHDC is 21.8% [73,74]. The NHDC market will grow at a CAGR of 4.6% from 2023 to 2030 [2].

5.1 Biosynthesis

Numerous biogenic studies have demonstrated that neohesperidin is a flavonoid-derived secondary metabolite, synthesised through the phenylpropanoid pathway [75,76]. This pathway begins with the deamination of phenylalanine by the enzyme phenylalanine ammonia-lyase (PAL) to produce trans-cinnamic acid. Cinnamic acid is then subsequently hydroxylated by cinnamate 4-hydroxylase to form 4-coumarate. The 4-coumarate then undergoes CoA esterification via 4-coumarate-CoA ligase to form 4-coumaroyl-CoA. One molecule of p-coumaroyl-CoA then combines with three molecules of malonyl-CoA to yield naringenin chalcone, catalyzed by chalcone synthase [77,78]. Chalcone isomerase (CHI) facilitates the conversion of naringenin chalcone to naringenin, and later to hesperetin (a flavanone aglycone). Glycosylation adds a disaccharide to the C7 hydroxyl group of the aglycone, improving bioavailability, stability and solubility. Research shows that neohesperidin is synthesized via glycosylation of flavonoid aglycones such as naringenin, hesperidin and hesperetin, converting them into glucosides and rhamnoglucosides. This process is catalyzed by the enzymes UDP-glucose-flavanone 7-O-glucosyltransferase and UDP-rhamnose flavanone [79]. Neohesperidin is usually extracted from citrus fruits and purified from neohesperidose, a disaccharide responsible for its bitterness. It has also been observed that neohesperidin is converted to neohesperidin dihydrochalcone by catalytic hydrogenation under alkaline conditions.

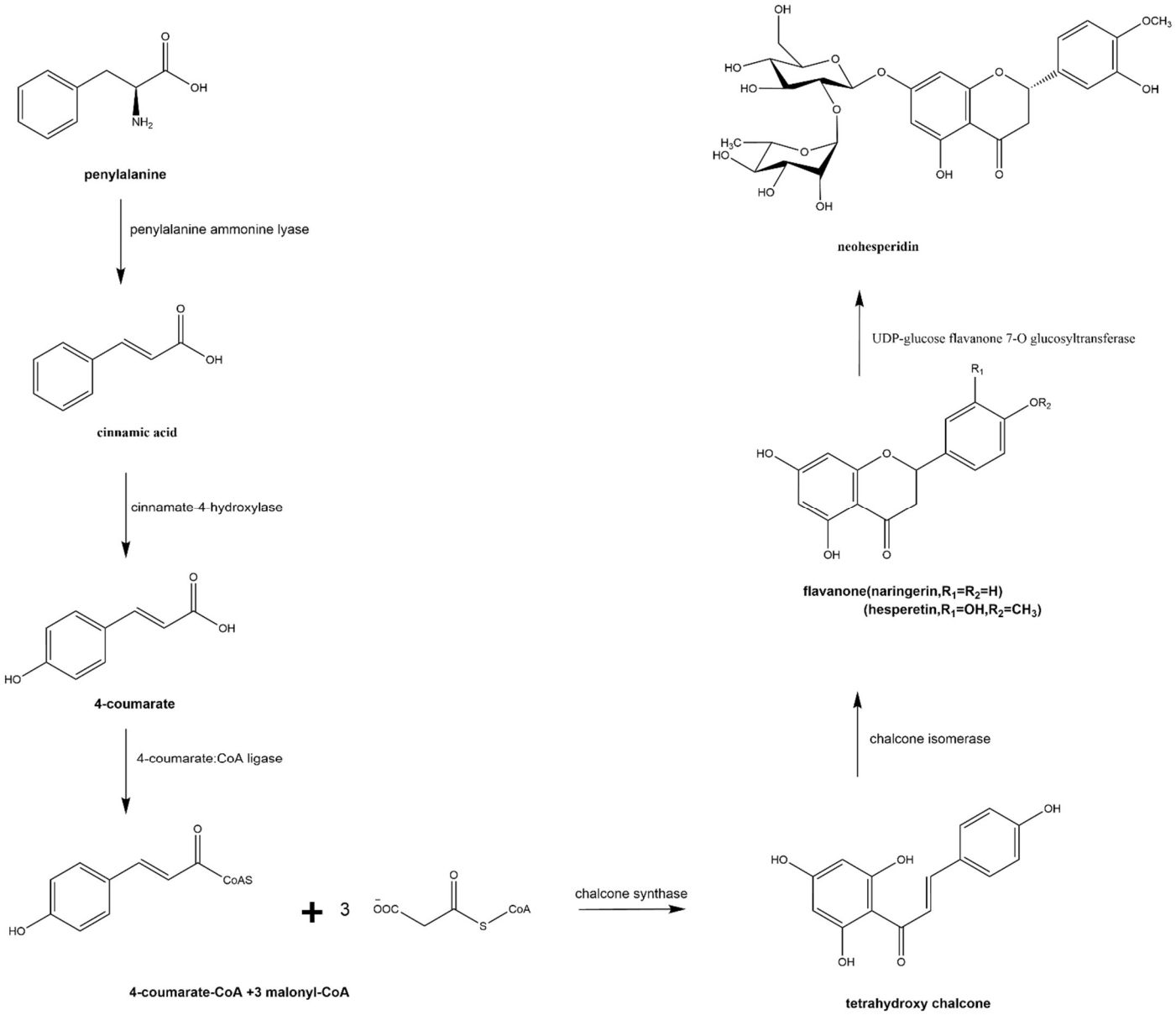

Figure 4. The biosynthesis process of neohesperidin.

5.2 Bioactive

Neohesperidin has demonstrated significant biological effects in various research areas, particularly in anti-inflammatory, antioxidant and metabolic regulation. In lipid metabolism, neohesperidin regulates the PI3K/AKT/mTOR pathway, effectively inhibiting adipocyte proliferation and reducing lipid accumulation. Adipocyte formation was reduced by approximately 25–30%, demonstrating its potential for obesity control [80]. In addition, in metabolic disorders induced by a high-fat diet, neohesperidin significantly reduced serum triglyceride and cholesterol levels, with triglycerides reduced by 30% and cholesterol by 25% [81]. Neohesperidin dihydrochalcone also significantly reduced blood glucose levels in rats fed a high-fat diet by 10%, reduced serum triglycerides by 25% and increased the abundance of the beneficial bacterium Coprococcus by 40% [82]. In addition, in animal studies,

neohesperidine improved cholesterol metabolism by reducing total cholesterol by 25%, low-density lipoprotein (LDL) by 20% and high-density lipoprotein (HDL) by 15% [83].

In obesity-related studies, neohesperidin dihydrochalcone was found to reduce fat cell production by 30%, leading to a 20% reduction in body fat and a 10% increase in lean body mass, while significantly inhibiting the PI3K/AKT/mTOR pathway [84]. Moreover, the combination of neohesperidin and rebaudioside A reduced visceral fat by 40%, decreased liver lipid levels by 20% and promoted an increase in beneficial gut bacteria in obese mice [85].

In food preservation, neohesperidin acts as a natural antioxidant, effectively delaying lipid oxidation. The oxidation process was reduced by 50%, extending the shelf life of foods and improving sensory qualities [86]. In milk preservation, neohesperidin extended the shelf life by approximately 30% due to its antioxidant and antimicrobial properties [87].

Neohesperidin's anti-inflammatory properties have been demonstrated in models of inflammation in the digestive system. In an experimental colitis model, neohesperidin dihydrochalcone reduced inflammation levels by 45% by inhibiting the expression of IL-6 and TNF-α, while oxidative stress markers decreased by 50% [82]. In dextran sulphate sodium-induced ulcerative colitis, neohesperidine reduced IL-1β, IL-6 and TNF-α levels by 30–40%, improved intestinal barrier function and reduced intestinal permeability by 20% [88]. These anti-inflammatory effects were further supported in models of gastrointestinal inflammation, where neohesperidin reduced overall intestinal inflammation scores by more than 30% [89].

In bone health, neohesperidine has been shown to promote osteogenic differentiation of bone marrow stromal cells (BMSCs). By regulating histone modifications of the lncRNA SNHG1, it increased alkaline phosphatase activity by 50% and mineralised nodule formation by 60% [90]. Neohesperidine also activated the Wnt/β-catenin pathway, increasing ALP activity by 45% and mineralised nodule formation by 35% [91]. It also promoted the proliferation of BMSCs, with proliferation rates increasing by 30% and osteogenic differentiation markers improving by 45% [92].

Neohesperidin also exhibited potential in neurodegenerative disease research, as it was shown to inhibit amyloid protein aggregation, with an inhibition rate of 50%, while reducing oxidative stress and neuronal apoptosis, suggesting its application in conditions such as Alzheimer’s disease [93]. Furthermore, in neuropathic pain models, neohesperidin alleviated mechanical hyperalgesia by regulating the P2X4 receptor, reducing pain scores by 50% [94].

Finally, in models of myocardial ischaemia-reperfusion injury, neohesperidine reduced cell apoptosis by 30% and oxidative stress (MDA) levels by 35% through inhibition of the JNK and NF-κB pathways [95].

In summary, neohesperidine exhibits a wide range of beneficial biological effects, particularly in lipid metabolism, anti-inflammation and bone health. Its ability to modulate key pathways, such as the PI3K/AKT/mTOR and Wnt/β-catenin pathways, together with its potent antioxidant and anti-inflammatory properties, positions it as a promising compound for the treatment of obesity, metabolic disorders, neurodegenerative diseases and inflammatory conditions. In addition, its potential

applications in food preservation and bone regeneration highlight its versatility and value across multiple therapeutic and industrial areas. Further research may unlock even more potential uses for neohesperidine, particularly in clinical settings.

6. Fructooligosaccharides

Fructooligosaccharides (FOS), sometimes called oligofructose or fructooligosaccharides, are oligosaccharides used as an alternative sweetener. The sweetness of FOS is between 30% and 50% of the sugar in commercial syrups [96]. FOS can be extracted from the blue agave plant and form fruits and vegetables such as bananas, onions, chicory root, garlic, asparagus, jícama, and leeks. Some grains and cereals, such as wheat and barley, also contain FOS [97]. Given the resistance of FOS to digestion due to the absence of brush border β-fructosidases, it can act as an excellent bulking agent due to its low caloric content (1–1.5 kcal/g), which has the potential to reduce energy intake by 65-75% compared to digestible carbohydrates [98,99]. This also means that FOS reaches the colon intact and acts as a prebiotic for beneficial microorganisms in the gut (bifidobacteria being the most commonly targeted group), providing health benefits to the host [99].

6.1 Biosynthesis

FOS synthesis is a complex biochemical process catalyzed by fructosyltransferases (FTases), which results in the formation of oligosaccharides with various structures. These oligosaccharides have wide applications in the food industry and biomedical fields due to their beneficial properties. FOS are short-chain oligosaccharides composed of sucrose and fructose units linked by different glycosidic bonds. Two key fructosyltransferases are involved in the synthesis of FOS: 1-FFT (1-fructosyltransferase) and 6-SFT (6-fructosyltransferase), each responsible for producing different types of FOS through different catalytic pathways.

1-FFT functions by transferring fructosyl groups from sucrose to another fructose or fructan polymer, forming new β(2→1) glycosidic bonds. Sucrose serves as the initial substrate, and 1-FFT catalyzes the transfer of fructose from sucrose to another fructose molecule, producing the simplest form of FOS, 1-kestose. The molecular structure of 1-kestose consists of a glucose molecule and two fructose units linked by β(2→1) glycosidic bonds. This step initiates the FOS synthesis process. As the reaction progresses, 1-FFT continues to add fructose units to 1-kestose, generating more complex FOS structures, such as 1-nystose, which contains additional fructose units. 1-nystose is often considered a precursor to inulin. Thus, 1-FFT plays a crucial role in the early stages of FOS synthesis, generating linear oligosaccharides linked by β(2→1) bonds.

6-SFT catalyzes more complex reactions, involving the formation of both β(2→1) and β(2→6) glycosidic bonds, which contribute to more intricate FOS structures. Unlike 1-FFT, which primarily forms linear fructan chains, 6-SFT is capable of synthesizing branched FOS. By catalyzing both β(2→1) and β(2→6) linkages, 6-SFT creates more diverse and complex oligosaccharides. For example, bifurcose is a representative product of 6-SFT catalysis. Its structure contains both β(2→1) and β(2→6) bonds, formed by first attaching a fructose molecule to sucrose via a β(2→1) bond, followed by the addition of another fructose molecule through a β(2→6) bond,

resulting in a more branched structure. This dual function of 6-SFT allows for the generation of more structurally diverse FOS.

Throughout the FOS synthesis process, 1-FFT and 6-SFT work together to produce a variety of FOS types with different degrees of complexity. 1-FFT primarily generates linear fructooligosaccharides, such as 1-kestose and 1-nystose, which are linked by β(2→1) bonds and form straight chains. In contrast, 6-SFT synthesizes both linear and branched FOS, such as bifurcose, by forming both β(2→1) and β(2→6) glycosidic bonds. The ability of 6-SFT to produce branched structures enhances the structural diversity of FOS and expands their potential applications.

Due to their unique structural properties, FOS synthesized by 1-FFT and 6-SFT have various functional applications. In the food industry, FOS are widely used as prebiotics that promote gut health by stimulating the growth of beneficial gut bacteria. Additionally, FOS serves as low-calorie sweeteners and dietary fiber supplements, providing health benefits without significantly impacting caloric intake. The ability to synthesize FOS with different structures also allows for the production of tailored oligosaccharides with specific functional properties suited for diverse industrial applications.

In conclusion, FOS synthesis is a process catalyzed by fructosyltransferases, which transfer fructose units to form oligosaccharides with various glycosidic bonds. 1-FFT mainly catalyzes the formation of FOS with β(2→1) bonds, resulting in linear structures, while 6-SFT can form both β(2→1) and β(2→6) bonds, generating branched FOS with more complex structures. The combined action of these two enzymes produces a wide range of FOS with different structural and biological functions.

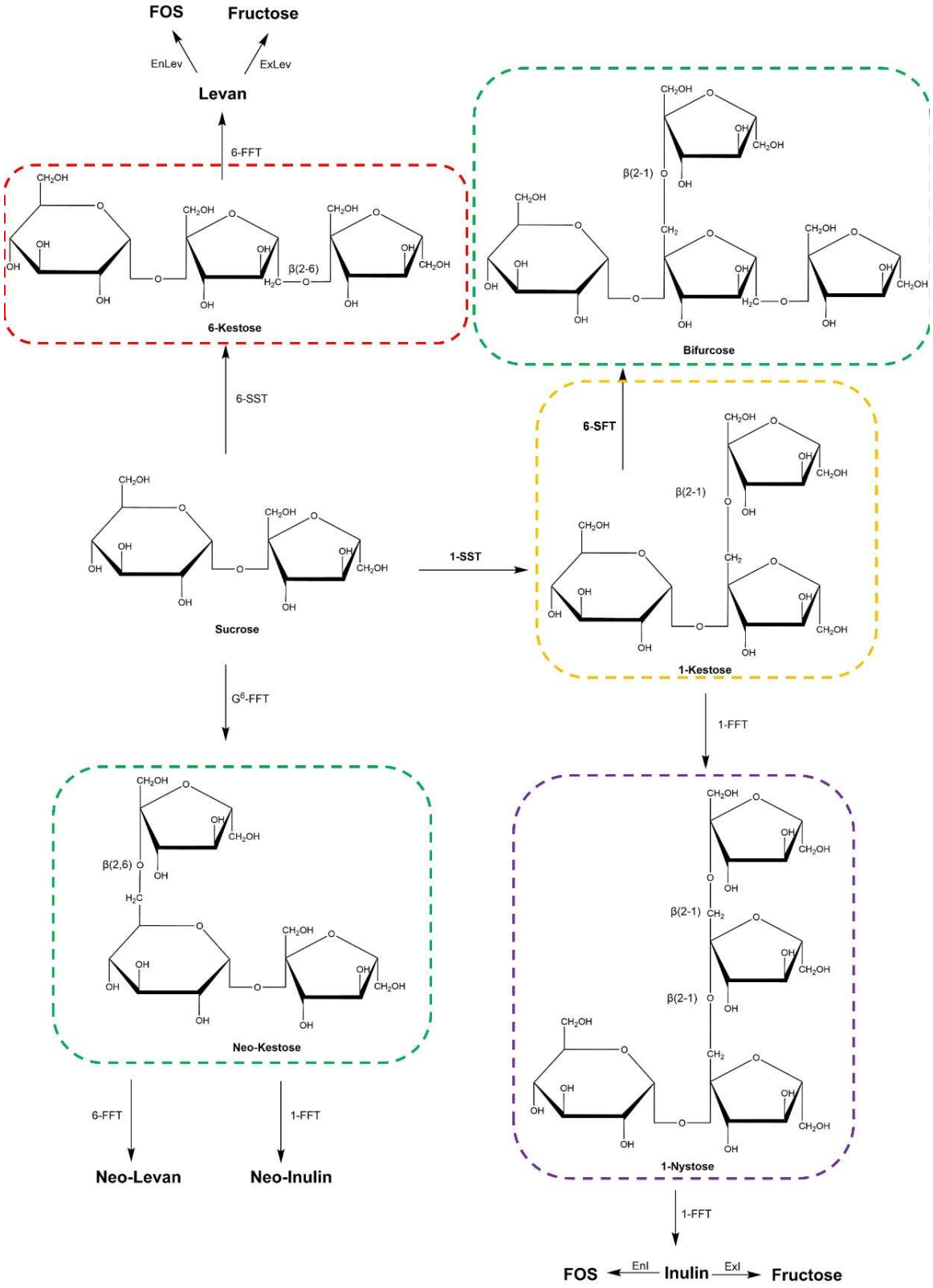

Fig 5. The biosynthesis process of fructooligosaccharides. 1-SST sucrose: sucrose 1-fructosyl-transferase; 1-FFT fructan: fructan 1-fructosyltransferase; 6-SST sucrose: sucrose 6-fructosyltransferase; 6-FFT fructan: fructan 6-fructosyltransferase, G6−FFT fructan: fructan 6G-fructosyltransferase; 6-SFT sucrose: fructan 6-fructosyltransferase; ExI exoinulinases; EnI endoinulinase; EnLev endolevanase; ExLev exolevanase

6.2 Bioactive

Fructooligosaccharides (FOS) have been extensively studied for their beneficial effects, particularly in relation to metabolic health, gut microbiota modulation, and inflammation reduction. FOS has been shown to promote the growth of beneficial gut bacteria, such as Bifidobacterium and Lactobacillus, while reducing harmful species like Clostridium difficile, resulting in improved gut health and reduced gastrointestinal discomfort [100,101]. This modulation of the gut microbiota also increases the production of short-chain fatty acids (SCFAs), particularly butyrate, which plays a key role in reducing inflammation and enhancing metabolic health [102,103].

In animal models, long-term FOS consumption has led to significant reductions in body weight and fat accumulation without changes in food intake, suggesting that FOS induces metabolic changes in the gut rather than limiting caloric intake [104,105]. Additionally, FOS has been found to reduce insulin resistance and systemic inflammation, demonstrating protective effects against metabolic syndrome. For example, in pregnant mice, FOS supplementation improved glucose tolerance and reduced obesity risk in their offspring, suggesting long-term metabolic benefits [106,107].

FOS also plays a crucial role in protecting liver health. Studies have shown that FOS supplementation reduces liver fat accumulation, improves lipid metabolism, and modulates gut-brain communication, offering protection against non-alcoholic fatty liver disease (NAFLD) [108,109]. Similarly, FOS has demonstrated protective effects on renal health, with studies showing reductions in oxidative stress and inflammatory markers in models of kidney injury, highlighting its potential as a therapeutic agent for kidney-related metabolic disorders [110].

Moreover, FOS shows synergistic effects when combined with other compounds. For example, the combination of FOS with galactooligosaccharides (GOS) enhances gut-brain axis signaling, while the combination of FOS and vitamin D3 significantly reduces intestinal inflammation and improves gut barrier function, suggesting broader therapeutic potential [111].

Studies have shown that ITF has a strong bifidobacterial effect on the human fecal microbiota and promotes the growth and activity of other bacteria known to have health benefits, such as Lactobacillus and F. prausnitzii. These effects on the gut microbiota contribute to human health and include improved intestinal barrier function, improved bowel movements, increased insulin sensitivity, lower blood triglycerides and improved lipid profiles, increased calcium and magnesium absorption, and increased satiety [112].

Collectively, these findings highlight the broad applications of FOS in managing metabolic diseases, promoting gut health, reducing inflammation, and potentially treating liver and kidney disorders. FOS is emerging as a valuable dietary supplement with both preventive and therapeutic applications, contributing to improved health outcomes in diverse populations [113,114].

7. Conclusion

In conclusion, natural sweeteners such as steviol glycosides, mogrosides, glycyrrhizin, neohesperidin, and fructooligosaccharides offer significant promise as

healthier alternatives to traditional sugars and artificial sweeteners. Their low or zero-calorie content, combined with various bioactive effects—including antioxidant, anti-inflammatory, and anti-diabetic properties—make them valuable in managing metabolic disorders like obesity and diabetes. The study of their biosynthetic pathways and pharmacological activities not only underscores their potential to promote human health but also paves the way for broader applications in the food, pharmaceutical, and nutraceutical industries. With the rising demand for functional, health-promoting ingredients, these natural sweeteners are well-positioned to play a key role in the development of health-conscious products. Future research should focus on optimizing their production methods and further exploring their long-term health effects to fully capitalize on their therapeutic potential.

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References

1. Bridel M. Opinion on stevioside as a sweetener. Scientific Committee on Food. 1931, 192, 1123–1125.
2. Benucci I., Lombardelli C., Esti M. A comprehensive review on natural sweeteners: impact on sensory properties, food structure, and new frontiers for their application. Critical Reviews in Food Science and Nutrition. 2024, 1–19. https://doi.org/10.1080/10408398.2024.2393204
3. Orellana-Paucar A.M. Steviol Glycosides from *Stevia rebaudiana*: An Updated Overview of Their Sweetening Activity, Pharmacological Properties, and Safety Aspects. Molecules. 2023, 28(3), 1258. https://doi.org/10.3390/molecules28031258
4. Zhou X., Gong M.Y., Lv X.Q., Liu Y.F., Li J.H., Du G.C., et al. Metabolic engineering for the synthesis of steviol glycosides: current status and future prospects. Applied Microbiology and Biotechnology. 2021, 105(13), 5367–5381. https://doi.org/10.1007/s00253-021-11419-3
5. Brandle J.E., Telmer P.G. Steviol glycoside biosynthesis. Phytochemistry. 2007, 68(14), 1855–1863. https://doi.org/10.1016/j.phytochem.2007.02.010
6. Rohmer M., Knani M,, Simonin P., Sutter B., Sahm H. Isoprenoid biosynthesis in bacteria: a novel pathway for the early steps leading to isopentenyl diphosphate. Biochemcal Journal. 1993, 295(2), 517–524. https://doi.org/10.1042/bj2950517
7. Totté N., Charon L., Rohmer M., Compernolle F., Baboeuf I., Geuns J.M.C. Biosynthesis of the diterpenoid steviol, an -kaurene derivative from Bertoni, via the methylerythritol phosphate pathway. Tetrahedron Letters. 2000, 41(39), 6407–6410. https://doi.org/10.1016/S0040-4039(00)01297-1
8. Lange B.M., Wildung M.R., McCaskill D., Croteau R. A family of transketolases that directs isoprenoid biosynthesis via a mevalonate-independent pathway. Proceedings of the National Academy of Sciences USA. 1998, 95(5), 2100–2104. https://doi.org/10.1073/pnas.95.5.2100
9. Pu X., Dong X., Li Q., Chen Z., Liu L. An update on the function and regulation of MEP and MVA pathways and their evolutionary dynamics. Journal of Integrative Plant Biology. 2021, 63, 1211–1226. https://doi.org/10.1111/jipb.13076
10. Wright L.P., Rohwer J.M., Ghirardo A., Hammerbacher A., Ortiz-Alcaide M., Raguschke B., et al. Deoxyxylulose 5-Phosphate Synthase Controls Flux through the Methylerythritol 4-Phosphate Pathway in Arabidopsis. Plant Physiology. 2014, 165(4), 1488–1504. https://doi.org/10.1104/pp.114.245191
11. Volke D.C., Rohwer J., Fischer R., Jennewein S. Investigation of the methylerythritol 4-phosphate pathway for microbial terpenoid production through metabolic control analysis. Microbial Cell Factories. 2019, 18(1), 192. https://doi.org/10.1186/s12934-019-1235-5

12. Kumar H., Singh K., Kumar S. 2C-methyl-d-erythritol 2,4-cyclodiphosphate synthase from Stevia rebaudiana Bertoni is a functional gene. Molecular Biology Reports. 2012, 39(12), 10971–10978. https://doi.org/10.1007/s11033-012-1998-9
13. Bongers M., Perez-Gil J., Hodson M.P., Schrübbers L., Wulff T., Sommer M.O.A, et al. Adaptation of hydroxymethylbutenyl diphosphate reductase enables volatile isoprenoid production. Elife. 2020, 9, e48685. https://doi.org/10.7554/eLife.48685
14. Totté N., Van den Ende W., Van Damme E.J.M., Compernolle F., Baboeuf I., Geuns J.M.C. Cloning and heterologous expression of early genes in gibberellin and steviol biosynthesis via the methylerythritol phosphate pathway in Stevia rebaudiana. Canadian Journal of Botany. 2003, 81(5), 517–522. https://doi.org/10.1139/B03-032
15. Gold N.D., Fossati E., Hansen C.C., DiFalco M., Douchin V., Martin V.J.J. A Combinatorial Approach To Study Cytochrome P450 Enzymes for De Novo Production of Steviol Glucosides in Baker's Yeast. ACS Synthetic Biology. 2018, 7(12), 2918–2929. https://doi.org/10.1021/acssynbio.8b00470
16. Kim K.K., Sawa Y., Shibata H. Hydroxylation of ent-kaurenoic acid to steviol in Stevia rebaudiana Bertoni--purification and partial characterization of the enzyme. Archives of Biochemistry and Biophysics. 1996, 332(2), 223–230. https://doi.org/10.1006/abbi.1996.0336
17. Dandin E., Ustundag U.V., Unal I., Ates-Kalkan P.S., Cansiz D., Beler M., et al. Stevioside ameliorates hyperglycemia and glucose intolerance, in a diet-induced obese zebrafish model, through epigenetic, oxidative stress and inflammatory regulation. Obesity Research Clinical Practice. 2022, 16(1), 23–29. https://doi.org/10.1016/j.orcp.2022.01.002
18. Kurek J.M., Krol E., Krejpcio Z. Steviol Glycosides Supplementation Affects Lipid Metabolism in High-Fat Fed STZ-Induced Diabetic Rats. Nutrients. 2020, 13(1), 112. https://doi.org/10.3390/nu13010112
19. Kurek J.M., Mikolajczyk-Stecyna J., Krejpcio Z. Steviol glycosides from Stevia rebaudiana Bertoni mitigate lipid metabolism abnormalities in diabetes by modulating selected gene expression - An in vivo study. Biomedicine Pharmacotherapy. 2023, 166, 115424. https://doi.org/10.1016/j.biopha.2023.115424
20. Kurek J.M., Zielinska-Wasielica J., Kowalska K., Krejpcio Z., Olejnik A. Modulating effects of steviol and steviol glycosides on adipogenesis, lipogenesis, glucose uptake and insulin resistance in 3T3-L1 adipocyte model. Journal of Functional Foods. 2022, 94, 105141. https://doi.org/10.1016/j.jff.2022.105141
21. Bai X.R., Qu H.Y., Zhang J.Y., Li L.K., Zhang C.F., Li S., et al. Effect of steviol glycosides as natural sweeteners on glucose metabolism in adult participants. Food Function. 2024, 15(8), 3908–3919. https://doi.org/10.1039/d3fo04695h
22. Kwok D., Scott C., Strom N., Fei A.Y., Lam C., Chakrabarti A., et al. Comparison of a Daily Steviol Glycoside Beverage compared with a Sucrose Beverage for Four Weeks on Gut Microbiome in Healthy Adults. The Journal of Nutrition. 2024, 154(4), 1298–1308. https://doi.org/10.1016/j.tjnut.2024.01.032
23. Raghavan G., Bapna A., Mehta A., Shah A., Vyas T. Effect of Sugar Replacement with Stevia-Based Tabletop Sweetener on Weight and Cardiometabolic Health among Indian Adults. Nutrients. 2023, 15(7), 1744. https://doi.org/10.3390/nu15071744
24. Yang L.F., Yang M.L., Zheng X.T., Ping Q., Song Y.F., Xie Y.F., et al. Selective biosynthesis and evaluation of rebaudioside M8 with improved organoleptic property and significant inhibition on inflammatory factor TNF-α. Food Bioscience. 2024, 59, 103898. https://doi.org/10.1016/j.fbio.2024.103898
25. Kurek J., Król E., Staniek H., Krejpcio Z. Steviol Glycoside, L-Arginine, and Chromium(III) Supplementation Attenuates Abnormalities in Glucose Metabolism in Streptozotocin-Induced Mildly Diabetic Rats Fed a High-Fat Diet. Pharmaceuticals. 2022, 15(10), 1200. https://doi.org/10.3390/ph15101200
26. Abdallah S.H., Mostafa N.M., Mohamed M.A., Nada A.S., Singab A.N.B. UPLC-ESI-MS/MS profiling and hepatoprotective activities of Stevia leaves extract, butanol fraction and stevioside against radiation-induced toxicity in rats. Natural Product Research. 2022, 36(21), 5619–5625. https://doi.org/10.1080/14786419.2021.2015594
27. Piatkowska E., Leszczynska T., Pieklo B., Kopec A., Biezanowska-Kopec R. Comparison of Steviol Glycosides or Stevia Leaves Addition to the Hypercholesterolemic Diet on Selected Biochemical Parameters of Experimental Rats. Applied Sciences. 2023, 13(22), 12364. https://doi.org/10.3390/app132212364
28. Noya-Leal F., van der Wielen N., Behrens M., Rouschop .S, van Arkel J., Jongsma M., et al. Rebaudioside A from stimulates GLP-1 release by enteroendocrine cells bitter taste signalling pathways. Food Function. 2023, 14(15), 6914–6928. https://doi.org/10.1039/d3fo00818e
29. Itkin M., Davidovich-Rikanati R., Cohen S., Portnoy V., Doron-Faigenboim A., Oren E., et al. The biosynthetic pathway of the nonsugar, high-intensity sweetener mogroside V from Siraitia grosvenorii. Proceedings of the National Academy of Sciences USA. 2016, 113(47), E7619–E7628. https://doi.org/10.1073/pnas.1604828113
30. Huang H., Peng Z., Zhan S., Li W., Liu D., Huang S., et al. A comprehensive review of Siraitia grosvenorii (Swingle) C. Jeffrey: chemical composition, pharmacology, toxicology, status of resources development, and applications. Frontiers in Pharmacology. 2024, 15, 1388747. https://doi.org/10.3389/fphar.2024.1388747
31. Qin X., Xiaojian S., Ronggan L., Yuxian W., Zhunian T., Shouji G., et al. Subchronic 90-day oral (Gavage) toxicity study of a Luo Han Guo mogroside extract in dogs. Food and Chemical Toxicology. 2006, 44(12), 2106–2109. https://doi.org/10.1016/j.fct.2006.07.023
32. Marone P.A., Borzelleca J.F., Merkel D., Heimbach J.T., Kennepohl E. Twenty eight-day dietary toxicity study of Luo Han fruit concentrate in Hsd:SD rats. Food and Chemical Toxicology. 2008, 46(3), 910–919. https://doi.org/10.1016/j.fct.2007.10.013

33. Chen N., Cao W., Yuan Y., Wang Y., Zhang X., Chen Y., et al. Recent advancements in mogrosides: A review on biological activities, synthetic biology, and applications in the food industry. Food Chemistry. 2024, 449, 139277. https://doi.org/10.1016/j.foodchem.2024.139277
34. Wang S.Y., Xu X.H., Lv X.Q., Liu Y.F., Li J.H., Du G.C., et al. Construction and Optimization of the Biosynthesis Pathway of Mogrol in Saccharomyces Cerevisiae. Frontiers in Bioengineering and Biotechnology. 2022, 10, 919526. https://doi.org/10.3389/fbioe.2022.919526
35. Wang C.H., Hou J., Deng H.K., Wang L.J. Microbial production of mevalonate. Journal of Biotechnology. 2023, 370, 1–11. https://doi.org/10.1016/j.jbiotec.2023.05.005
36. Wang Q., Quan S., Xiao H. Towards efficient terpenoid biosynthesis: manipulating IPP and DMAPP supply. Bioresources and Bioprocessing. 2019, 6. https://doi.org/10.1186/s40643-019-0242-z
37. Oldfield E., Lin F.Y. Terpene Biosynthesis: Modularity Rules. Angewandte Chemie International Edition. 2012, 51(5), 1124–1137. https://doi.org/10.1002/anie.201103110
38. Methods and materials for biosynthesis of mogroside compounds. Available online: https://pubchem.ncbi.nlm.nih.gov/patent/US-10011859-B2 (accessed on 27 December 2024).
39. Zhang Y.L., Zhou G.S., Peng Y., Wang M.Y., Li X.B. Anti-hyperglycemic and anti-hyperlipidemic effects of a special fraction of Luohanguo extract on obese T2DM rats. Journal of Ethnopharmacology. 2020, 247, 112273. https://doi.org/10.1016/j.jep.2019.112273
40. Zhang Y.L., Peng Y., Zhao L.J., Zhou G.S., Li X.B. Regulating the gut microbiota and SCFAs in the faeces of T2DM rats should be one of antidiabetic mechanisms of mogrosides in the fruits of. Journal of Ethnopharmacology. 2021, 274, 112273. https://doi.org/10.1016/j.jep.2021.114033
41. Dou T., Wang J., Liu Y.S., Jia J.G., Zhou L.W., Liu G.X., et al. A Combined Transcriptomic and Proteomic Approach to Reveal the Effect of Mogroside V on OVA-Induced Pulmonary Inflammation in Mice. Frontiers in Immunology. 2022, 13, 800143. https://doi.org/10.3389/fimmu.2022.800143
42. Lü W.C., Ren G.Q., Shimizu K., Li R.S., Zhang C.F. Mogroside IIE, an metabolite of sweet agent, alleviates acute lung injury via Pla2g2a-EGFR inhibition. Food Science and Human Wellness. 2024, 13(1), 299–312. https://doi.org/10.26599/Fshw.2022.9250025
43. Mo Q.T., Fu H., Zhao D., Zhang J.C., Wang C.T., Wang D.D., et al. Protective Effects of Mogroside V on Oxidative Stress Induced by HO in Skin Fibroblasts. Drug Design, Development and Therapy. 2021, 15, 4901–4909. https://doi.org/10.2147/Dddt.S337524
44. Li Y.M., Chen Y.D., Wei M.L., Wei C.H. Preclinical Evidence Indicates the Pharmacological Targets and Mechanisms of Mogroside V in Patients With Ovarian Cancer and Coronavirus Disease 2019. Frontiers in Endocrinology. 2022, 13, 84540. https://doi.org/10.3389/fendo.2022.845404
45. Sec. 184.1408 Licorice and licorice derivatives. Available online: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=184.1408 (accessed on 11 November 2024).
46. Guo X., Li T., Tang K., Liu R.H. Effect of Germination on Phytochemical Profiles and Antioxidant Activity of Mung Bean Sprouts (*Vigna radiata*). Journal of Agricultural and Food Chemistry. 2012, 60(44), 11050–11055. https://doi.org/10.1021/jf304443u
47. Singh D., Gupta R., Saraf S.A. Herbs–are they safe enough? An overview. Critical Reviews in Food Science and Nutrition. 2012, 52(10), 876–898. https://doi.org/10.1080/10408398.2010.512426
48. Isbrucker R., Burdock G. Risk and safety assessment on the consumption of Licorice root (Glycyrrhiza sp.), its extract and powder as a food ingredient, with emphasis on the pharmacology and toxicology of glycyrrhizin. Regulatory Toxicology and Pharmacology. 2006, 46(3), 167–192. https://doi.org/10.1016/j.yrtph.2006.06.002
49. Sigurjonsdottir H., Manhem K., Axelson M., Wallerstedt SJJohh. Subjects with essential hypertension are more sensitive to the inhibition of 11 β-HSD by liquorice. Journal of Human Hypertension. 2003, 17(2), 125–131. https://doi.org/10.1038/sj.jhh.100150
50. Han Y.X., Jia Q.J., Yang D.F., Chai W.G., Zhang X.M., He Q.L., et al. Current advances in environmental stimuli regulating the glycyrrhizic acid biosynthesis pathway. Fitoterapia. 2021, 151, 104860. https://doi.org/10.1016/j.fitote.2021.104860
51. Christianson D.W. Unearthing the roots of the terpenome. Current Opinion in Chemical Biology. 2008, 12(2), 141–150. https://doi.org/10.1016/j.cbpa.2007.12.008
52. Li Y., Niu Y., Song J., Luo H., Li. Q., Sun C. Development of the Devices for Synthetic Biology of Glycyrrhizin at an Early Stage: Cloning and Sequencing Analysis of Farnesyl-Diphosphate Synthase Genes in Glycyrrhiza uralensis. World Science and Technology-Modernization of Traditional Chinese Medicine. 2013, 3, 355–359.
53. Liu Y., Zhang N., Chen H., Gao Y., Wen H., Liu Y., Liu C. Cloning and characterization of two cDNA sequences coding squalene synthase involved in glycyrrhizic acid biosynthesis in Glycyrrhiza uralensis. Frontier and Future Development of Information Technology in Medicine and Education. 2014, 269, 329–342. https://doi.org/10.1007/978-94-007-7618-0_32
54. Hayashi H., Huang P., Kirakosyan A., Inoue K., Hiraoka N., Ikeshiro Y., Kushiro T., Shibuya M., Ebizuka Y. Cloning and characterization of a cDNA encoding β-amyrin synthase involved in glycyrrhizin and soyasaponin biosyntheses in licorice. Biological and Pharmaceutical Bulletin. 2001, 24(8), 912–916. https://doi.org/10.1248/bpb.24.912

55. Chen H., Liu Y., Zhang X., Zhan X., Liu C. Cloning and characterization of the gene encoding β-amyrin synthase in the glycyrrhizic acid biosynthetic pathway in Glycyrrhiza uralensis. Acta Pharmaceutica Sinica B. 2013, 3(6), 416–424. https://doi.org/10.1016/j.apsb.2013.09.002
56. Seki H., Ohyama K., Sawai S., Mizutani M., Ohnishi T., Sudo H., Akashi T., Aoki T., Saito K., Muranaka T. Licorice β-amyrin 11-oxidase, a cytochrome P450 with a key role in the biosynthesis of the triterpene sweetener glycyrrhizin. Proceedings of the National Academy of Sciences USA. 2008, 105(37), 14204–14209. https://doi.org/10.1073/pnas.0803876105
57. Seki H., Sawai S., Ohyama K., Mizutani M., Ohnishi T., Sudo H., et al. Triterpene functional genomics in licorice for identification of CYP72A154 involved in the biosynthesis of glycyrrhizin. The Plant Cell. 2011, 23(11), 4112–4123. https://doi.org/10.1105/tpc.110.082685
58. Xu G.J., Cai W., Gao W., Liu C.S. A novel glucuronosyltransferase has an unprecedented ability to catalyse continuous two-step glucuronosylation of glycyrrhetinic acid to yield glycyrrhizin. New Phytologist. 2016, 212(1), 123–135. https://doi.org/10.1111/nph.14039
59. Ageeva A.A., Kruppa A.I., Magin I.M., Babenko S.V., Leshina T.V., Polyakov N.E. New Aspects of the Antioxidant Activity of Glycyrrhizin Revealed by the CIDNP Technique. Antioxidants. 2022, 11(8), 1591. https://doi.org/10.3390/antiox11081591
60. Ban J.Y., Park H.K., Kim S.K. Effect of Glycyrrhizic Acid on Scopolamine-Induced Cognitive Impairment in Mice. International Neurourology Journal. 2020, 24(Suppl 1), S48–55. https://doi.org/10.5213/inj.2040154.077
61. Wang H., Li R., Rao Y., Liu S., Hu C., Zhang Y., et al. Enhancement of the Bioavailability and Anti-Inflammatory Activity of Glycyrrhetinic Acid via Novel Soluplus((R))-A Glycyrrhetinic Acid Solid Dispersion. Pharmaceutics. 2022, 14(9), 1797. https://doi.org/10.3390/pharmaceutics14091797
62. Song Y.-L, Liu H.-W., Yang Y.-H., He J.-J., Yang B.-X., Yang L.-L., et al. Novel 18β-glycyrrhetinic acid amide derivatives show dual-acting capabilities for controlling plant bacterial diseases through ROS-mediated antibacterial efficiency and activating plant defense responses. Journal of Integrative Agriculture. 2023, 22(9), 2759–2771. https://doi.org/10.1016/j.jia.2022.10.009
63. Baltina L.A., Hour M.-J., Liu Y.-C., Chang Y.-S., Huang S.-H., Lai H.-C., et al. Antiviral activity of glycyrrhizic acid conjugates with amino acid esters against Zika virus. Virus Research. 2021, 294, 198290. https://doi.org/10.1016/j.virusres.2020.198290
64. Sun J., Liu H.Y., Lv C.Z., Qin J., Wu Y.F. Modification, Antitumor Activity, and Targeted PPARgamma Study of 18beta-Glycyrrhetinic Acid, an Important Active Ingredient of Licorice. Journal of Agricultural and Food Chemistry. 2019, 67(34), 9643–9651. https://doi.org/10.1021/acs.jafc.9b03442
65. Polyakov N.E., Leshina T.V. Physicochemical Approaches to the Study of the Antioxidant Activity of Glycyrrhizin. Russian Journal of Physical Chemistry A. 2023, 97(5), 828–835. https://doi.org/10.1134/s0036024423050229
66. Tu B., Liang J., Ou Y., Zhang X., Zheng W., Wu R., et al. Novel 18beta-glycyrrhetinic acid derivatives as a Two-in-One agent with potent antimicrobial and anti-inflammatory activity. Bioorganic Chemistry. 2022, 122, 105714. https://doi.org/10.1016/j.bioorg.2022.105714
67. Wen Y., Chen H., Zhang L., Wu M., Zhang F., Yang D., et al. Glycyrrhetinic acid induces oxidative/nitrative stress and drives ferroptosis through activating NADPH oxidases and iNOS, and depriving glutathione in triple-negative breast cancer cells. Free Radical Biology and Medicine. 2021, 173, 41–51. https://doi.org/10.1016/j.freeradbiomed.2021.07.019
68. Bian M., Zhen D., Shen Q.K., Du H.H., Ma Q.Q., Quan Z.S. Structurally modified glycyrrhetinic acid derivatives as anti-inflammatory agents. Bioorganic Chemistry. 2021, 107, 104598. https://doi.org/10.1016/j.bioorg.2020.104598
69. Lee J.C., Seksama L.H., Park C.H., Kim C.S. Enhancing the anti-bacterial activity of nanofibrous polyurethane membranes by incorporating glycyrrhizic acid-conjugated β-Cyclodextrin. Materials Letters. 2023, 338, 134030. https://doi.org/10.1016/j.matlet.2023.134030
70. Hu H.C., Lei Y.H., Zhang W., Xiong P.Y., Song L., Luo X.Q., et al. Anti-inflammatory activity and safety of compound glycyrrhizin in ulcerative colitis: A systematic review and meta-analysis of randomized controlled trials. Journal of Functional Foods. 2022, 91, 105004. https://doi.org/10.1016/j.jff.2022.105004
71. Liao W., Wu H., Pang L., He B., Tong J., Qin J., et al. *Hylocereus undatus* flower suppresses DSS-induced colitis in mice by reducing intestinal inflammation, repairing the intestinal physical barrier, and modulating gut and lung microbiota. Journal of Functional Foods. 2023, 110, 105820. https://doi.org/10.1016/j.jff.2023.105820
72. Zhou S., Liu G., Si Z., Yu L., Hou L. Glycyrrhizin, an HMGB1 inhibitor, Suppresses Interleukin-1beta-Induced Inflammatory Responses in Chondrocytes from Patients with Osteoarthritis. Cartilage. 2021, 13(2_suppl), 947S–955S. https://doi.org/10.1177/1947603520934858
73. Wang R., You W., Lin H., Cao Y., Xu C., Chen K., et al. Naringin, neohesperidin and their corresponding dihydrochalcones as bioactive substances: a symphony of bitter–sweet. Food Quality and Safety. 2023, 7, fyad036. https://doi.org/10.1093/fqsafe/fyad036
74. Younes M., Aquilina G., Castle L., Degen G., et al. Re-evaluation of neohesperidine dihydrochalcone (E 959) as a food additive. EFSA Journal. 2022, 20(11), e07595. https://doi.org/10.2903/j.efsa.2022.7595
75. Akhter S., Arman M.S.I., Tayab M.A., Islam M.N., Xiao J. Recent advances in the biosynthesis, bioavailability, toxicology, pharmacology, and controlled release of citrus neohesperidin. Critical Reviews in Food Science and Nutrition. 2024, 64(15), 5073–5092. https://doi.org/10.1080/10408398.2022.2149466

76. Frydman A., Weisshaus O., Huhman D.V., Sumner L.W., Bar-Peled M., Lewinsohn E., et al. Metabolic engineering of plant cells for biotransformation of hesperedin into neohesperidin, a substrate for production of the low-calorie sweetener and flavor enhancer NHDC. Journal of Agricultural and Food Chemistry. 2005, 53(25), 9708–9712. https://doi.org/10.1021/jf051509m
77. Chaudhary P.R., Bang H., Jayaprakasha G.K., Patil B.S. Variation in Key Flavonoid Biosynthetic Enzymes and Phytochemicals in 'Rio Red' Grapefruit (Citrus paradisi Macf.) during Fruit Development. Journal of Agricultural and Food Chemistry. 2016, 64(47), 9022–9032. https://doi.org/10.1021/acs.jafc.6b02975
78. Khan M.K., Zill-E-Huma, Dangles O. A comprehensive review on flavanones, the major citrus polyphenols. Journal of Food Composition and Analysis. 2014, 33(1), 85–104. https://doi.org/10.1016/j.jfca.2013.11.004
79. Sharma K., Mahato N., Lee Y.R. Extraction, characterization and biological activity of citrus flavonoids. Reviews in Chemical Engineering. 2019, 35(2), 265–284. https://doi.org/10.1515/revce-2017-0027
80. Sage J., Renault J., Domain R., Bojarski K.K., Chazeirat T., Saidi A., et al. Modulation of the expression and activity of cathepsin S in reconstructed human skin by neohesperidin dihydrochalcone. Matrix Biology. 2022, 107, 97–112. https://doi.org/10.1016/j.matbio.2022.02.003
81. Deyama S., Aoki S., Sugie R., Kaneda K. Neohesperidin exerts antidepressant-like effect via the mechanistic target of rapamycin complex 1 in the medial prefrontal cortex in male mice. Journal of Pharmacological Sciences. 2024, 156(2), 82–85. https://doi.org/10.1016/j.jphs.2024.07.010
82. Erdem I., Aktas S., Ogut S. Neohesperidin Dihydrochalcone Ameliorates Experimental Colitis via Anti-Inflammatory, Antioxidative, and Antiapoptosis Effects. Journal of Agricultural and Food Chemistry. 2024, 72(28), 15715–15724. https://doi.org/10.1021/acs.jafc.4c02731
83. Huang Y., Tocmo R., Nauman M.C., Haughan M.A., Johnson J.J. Defining the Cholesterol Lowering Mechanism of Bergamot (Citrus bergamia) Extract in HepG2 and Caco-2 Cells. Nutrients. 2021, 13(9), 3156. https://doi.org/10.3390/nu13093156
84. Kwon M., Kim Y., Lee J., Manthey J.A., Kim Y., Kim Y. Neohesperidin Dihydrochalcone and Neohesperidin Dihydrochalcone-O-Glycoside Attenuate Subcutaneous Fat and Lipid Accumulation by Regulating PI3K/AKT/mTOR Pathway In Vivo and In Vitro. Nutrients. 2022, 14(5), 1087. https://doi.org/10.3390/nu14051087
85. Kim Y., Han H., Oh Y., Shin H., Park G., Park S., et al. A combination of rebaudioside A and neohesperidin dihydrochalcone suppressed weight gain by regulating visceral fat and hepatic lipid metabolism in ob/ob mice. Food Science and Biotechnology. 2024, 33(4), 913–923. https://doi.org/10.1007/s10068-023-01391-1
86. Wang Y., Jin R., Chen J., Cao J., Xiao J., Li X., et al. Tangeretin maintains antioxidant activity by reducing CUL3 mediated NRF2 ubiquitination. Food Chemistry. 2021, 365, 130470. https://doi.org/10.1016/j.foodchem.2021.130470
87. Yang R., Qi L., Liang W. Neohesperidin dihydrochalbazone protects against septic acute kidney injury in mice. Phytomedicine. 2023, 110, 154623. https://doi.org/10.1016/j.phymed.2022.154623
88. Ju T., Song Z., Qin D., Cheng J., Li T., Hu G., et al. Neohesperidin Attenuates DSS-Induced Ulcerative Colitis by Inhibiting Inflammation, Reducing Intestinal Barrier Damage, and Modulating Intestinal Flora Composition. Journal of Agricultural and Food Chemistry. 2024, 72(37), 20419–20431. https://doi.org/10.1021/acs.jafc.4c04433
89. Zhang J., Hui Y., Liu F., Yang Q., Lu Y., Chang Y., et al. Neohesperidin Protects Angiotensin II-Induced Hypertension and Vascular Remodeling. Frontiers in Pharmacology. 2022, 13, 890202. https://doi.org/10.3389/fphar.2022.890202
90. Zhang C., Yuan S., Chen Y., Wang B. Neohesperidin promotes the osteogenic differentiation of human bone marrow stromal cells by inhibiting the histone modifications of lncRNA SNHG1. Cell Cycle. 2021, 20(19), 1953–1966. https://doi.org/10.1080/15384101.2021.1969202
91. Chang Y.W., Zhu W.J., Gu W., Sun J., Li Z.Q., Wei X.E. Neohesperidin promotes the osteogenic differentiation of bone mesenchymal stem cells by activating the Wnt/beta-catenin signaling pathway. Journal of Orthopaedic Surgery and Research. 2021, 16(1), 334. https://doi.org/10.1186/s13018-021-02468-5
92. Yuan S., Zhang C., Wang B. Neohesperidin promotes the proliferation and osteogenic differentiation of BMSCs via BMP2-Wnt/beta-catenin pathway. Cell Cycle. 2022, 21(2), 187–201. https://doi.org/10.1080/15384101.2021.2015668
93. Chakraborty S., Rakshit J., Bandyopadhyay J., Basu S. Multi-target inhibition ability of neohesperidin dictates its neuroprotective activity: Implication in Alzheimer's disease therapeutics.International Journal of Biological Macromolecules. 2021, 176, 315–324. https://doi.org/10.1016/j.ijbiomac.2021.02.073
94. Wang Y., Li C., Xing J., Zhu Y., Sun M., Yin S., et al. Neohesperidin Alleviates the Neuropathic Pain Behavior of Rats by Downregulating the P2X4 Receptor. Neurochemical Research. 2023, 48(3), 781–790. https://doi.org/10.1007/s11064-022-03805-8
95. Li A., Zhang X., Luo Q. Neohesperidin alleviated pathological damage and immunological imbalance in rat myocardial ischemia-reperfusion injury via inactivation of JNK and NF-kappaB p65. Bioscience, Biotechnology, and Biochemistry. 2021, 85(2), 251–261. https://doi.org/10.1093/bbb/zbaa064
96. Cheng Y., Xiang N., Cheng X., Chen H., Guo X. Effect of photoperiod on polyphenol biosynthesis and cellular antioxidant capacity in mung bean (*Vigna radiata*) sprouts. Food Research International. 2022, 159, 111626. https://doi.org/10.1016/j.foodres.2022.111626
97. Campbell J.M., Bauer L.L., Fahey G.C., et al. Selected Fructooligosaccharide (1-Kestose, Nystose, and 1F-β-Fructofuranosylnystose) Composition of Foods and Feeds. Journal of Agricultural and Food Chemistry. 1997, 45 (8), 3076–3082. https://doi.org/10.1021/jf970087g

98. Soukoulis C, Fisk I. Innovative ingredients and emerging technologies for controlling ice recrystallization, texture, and structure stability in frozen dairy desserts: A review. Critical Reviews in Food Science and Nutrition. 2016, 56(15), 2543–2559. https://doi.org/10.1080/10408398.2013.876385
99. Jackson P.P.J., Wijeyesekera A., Rastall R.A. Inulin-type fructans and short-chain fructooligosaccharides-their role within the food industry as fat and sugar replacers and texture modifiers-what needs to be considered! Food Science and Nutrition. 2023, 11(1), 17–38. https://doi.org/10.1002/fsn3.3040
100. Dou Y., Yu X., Luo Y., Chen B., Ma D., Zhu J. Effect of Fructooligosaccharides Supplementation on the Gut Microbiota in Human: A Systematic Review and Meta-Analysis. Nutrients. 2022, 14(16), 3298. https://doi.org/10.3390/nu14163298
101. Tavares L.M., de Jesus L.C.L., Batista V.L., Barroso F.A.L., dos Santos Freitas A., Campos G.M., et al. Synergistic synbiotic containing fructooligosaccharides and Lactobacillus delbrueckii CIDCA 133 alleviates chemotherapy-induced intestinal mucositis in mice. World Journal of Microbiology and Biotechnology. 2023, 39(9), 235. https://doi.org/10.1007/s11274-023-03679-0
102. Costa G.T., Vasconcelos Q.D.J.S., Aragão G.F. Fructooligosaccharides on inflammation, immunomodulation, oxidative stress, and gut immune response: a systematic review. Nutrition Reviews. 2022, 80(4), 709–722. https://doi.org/10.1093/nutrit/nuab115
103. Gelineau A., Marcelin G., Ouhachi M., Dussaud S., Voland L., Manuel R., et al. Fructooligosaccharides benefits on glucose homeostasis upon high-fat diet feeding require type 2 conventional dendritic cells. Nature Communications. 2024, 15(1), 5413. https://doi.org/10.1038/s41467-024-49820-x
104. Cui S., Guo W., Chen C., Tang X., Zhao J., Mao B., et al. Metagenomic Analysis of the Effects of Lactiplantibacillus plantarum and Fructooligosaccharides (FOS) on the Fecal Microbiota Structure in Mice. Foods. 2022, 11(9), 1187. https://doi.org/10.3390/foods11091187
105. Paone P., Suriano F., Jian C., Korpela K., Delzenne N.M., Van Hul M., et al. Prebiotic oligofructose protects against high-fat diet-induced obesity by changing the gut microbiota, intestinal mucus production, glycosylation and secretion. Gut Microbes. 2022, 14(1), 2152307. https://doi.org/10.1080/19490976.2022.2152307
106. Almasri F., Collotta D., Aimaretti E., Sus N., Aragno M., Dal Bello F., et al. Dietary Intake of Fructooligosaccharides Protects against Metabolic Derangements Evoked by Chronic Exposure to Fructose or Galactose in Rats. Molecular Nutrition Food Research. 2024, 68(4), e2300476. https://doi.org/10.1002/mnfr.202300476
107. Miyamoto J., Ando Y., Nishida A., Yamano M., Suzuki S., Takada H., et al. Fructooligosaccharides Intake during Pregnancy Improves Metabolic Phenotype of Offspring in High Fat Diet-Induced Obese Mice. Molecular Nutrition Food Research. 2024, 68(9), e2300758. https://doi.org/10.1002/mnfr.202300758
108. Huang X., Chen Q., Fan Y., Yang R., Gong G., Yan C., et al. Fructooligosaccharides attenuate non-alcoholic fatty liver disease by remodeling gut microbiota and association with lipid metabolism. Biomedicine Pharmacotherapy. 2023, 159, 114300. https://doi.org/10.1016/j.biopha.2023.114300
109. Silva R.S.D., Mendonca I.P., Paiva I.H.R., Souza J.R.B., Peixoto C.A. Fructooligosaccharides and galactooligosaccharides improve hepatic steatosis via gut microbiota-brain axis modulation. International Journal of Food Sciences and Nutrition. 2023, 74(7), 760–780. https://doi.org/10.1080/09637486.2023.2262779
110. Pengrattanachot N., Thongnak L., Promsan S., Phengpol N., Sutthasupha P., Tocharus J., et al. Fructooligosaccharides Ameliorate Renal Injury and Dysfunction Through the Modulation of Gut Dysbiosis, Inhibition of Renal Inflammation, Oxidative Stress, Fibrosis, and Improve Organic Anion Transporter 3 Function in an Obese Rat Model. Molecular Nutrition Food Research. 2024, 68(16), e2400191. https://doi.org/10.1002/mnfr.202400191
111. Hanson T., Constantine E., Nobles Z., Butler E., Renteria K.M., Teoh C.M., et al. Supplementation of Vitamin D(3) and Fructooligosaccharides Downregulates Intestinal Defensins and Reduces the Species Abundance of Romboutsia ilealis in C57BL/6J Mice. Nutrients. 2024, 16(14), 2236. https://doi.org/10.3390/nu16142236
112. Hughes R.L., Alvarado D.A., Swanson K.S., Holscher H.D. The Prebiotic Potential of Inulin-Type Fructans: A Systematic Review. Advances in Nutrition. 2022, 13(2), 492–529. https://doi.org/10.1093/advances/nmab119
113. Dallali D., Fakhfakh J., Paris C., Hamden K., Varbanov M., Allouche N. Fructooligosaccharides from Cynoglossum tubiflorus: Effect of the molecular size on their antidiabetic activity in high-fat diet and alloxan induced diabetic rats. Bioorganic Chemistry. 2024, 143, 107100. https://doi.org/10.1016/j.bioorg.2024.107100
114. Pengrattanachot N., Thongnak L., Lungkaphin A. The impact of prebiotic fructooligosaccharides on gut dysbiosis and inflammation in obesity and diabetes related kidney disease. Food Function. 2022, 13(11), 5925–5945. https://doi.org/10.1039/d1fo04428a