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Review Article

A Comprehensive Review on Extraction, Structure, Detection, Bioactivity, and Metabolism of Flavonoids from Sea Buckthorn (*Hippophae rhamnoides* L.)

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Sea buckthorn (*Hippophae rhamnoides* L.) is an important plant with homology of medicine and food. It has rich nutritional and medicinal properties. It is used as a traditional Chinese medicine with therapeutic functions of invigorating spleen, relieving cough, eliminating food, eliminating phlegm, dispersing blood stasis, and promoting blood circulation. This review comprehensively summarized flavonoids from sea buckthorn (*Hippophae rhamnoides* L.), including extraction methods (solvent extraction, ultrasound-assisted extraction, microwave-assisted extraction, enzyme-assisted extraction, and collaborative extraction), two structure types (18 flavone aglycones and 81 flavone glycosides), detection methods (UV, HPLC, and NMR), bioactivities (antiviral, anti-inflammatory, hepatoprotective, weight-reducing, and hypoglycemic activities), and physiological metabolisms (most of flavonoids are converted into small molecule monophenolic acids through intestinal microbial catabolism). It will supply an important theoretical basis and valuable reference for researching and exploiting sea buckthorn (*Hippophae rhamnoides* L.) in the future. *Practical Applications*. Sea buckthorn (*Hippophae rhamnoides* L.) is an edible and medical plant with many functional properties. A comprehensive review on extraction, structure, detection, bioactivity, and metabolism of flavonoids from sea buckthorn (*Hippophae rhamnoides* L.) was made in this paper. This review will provide an important foundation for further studies of sea buckthorn (*Hippophae rhamnoides* L.) focusing on its development and utilization.

1. Introduction

Sea buckthorn (*Hippophae rhamnoides* L.) belongs to the Elaeagnaceae family [1]. It is not only used as a favorite fruit with rich nutrients but also served as a medicinal plant with multiple medical functions of invigorating spleen, relieving cough, eliminating food, eliminating phlegm, dispersing blood stasis, and promoting blood circulation [2]. There are 7 species and 11 subspecies of *Hippophae* L. in the world. Moreover, 7 species and 7 subspecies of *Hippophae* L. were distributed in China with a total area of about 2.7 million hm^2, accounting for more than 90% of the growth area of sea buckthorn in the world. Above species and subspecies are mainly distributed in 19 provinces such as Xinjiang, Inner Mongolia, Ningxia, Qinghai, and Gansu of China [3]. Previous phytochemical studies revealed that sea buckthorn (*Hippophae rhamnoides* L.) contained many types of compounds, including flavonoids, lignans, tannins, terpenoids, steroids, alkaloids, volatile oils, and organic acids [4, 5]. Among them, flavonoids were the most abundant active components in sea buckthorn. Most of flavonoids were glycosides synthesized by sugars, while a small number of

them existed in the form of free aglycones [6, 7]. Modern pharmacological studies have exhibited that these compounds have a variety of pharmacological activities [8, 9] and are of great significance for the treatment and prevention of many human diseases. At present, although sea buckthorn (*Hippophae rhamnoides* L.) has been reported by a large number of studies about phytochemicals and bioactivities in the world, this paper mainly reviews the extraction, structure, detection, bioactivity, and metabolism of flavonoids in sea buckthorn (*Hippophae rhamnoides* L.), which is different from the reported relevant references. Therefore, it is concluded that sea buckthorn (*Hippophae rhamnoides* L.) has a good development prospect and utilization value in the field of medical research. In order to deeply find some new active constituents from sea buckthorn (*Hippophae rhamnoides* L.) in the future, an updated review on extraction, structure, detection, bioactivity, and metabolism of flavonoids from sea buckthorn (*Hippophae rhamnoides* L.) is summarized and analyzed in this paper. This review will be of great significance for the future exploitation and utilization development of the sea buckthorn (*Hippophae rhamnoides* L.), which provides some important insights and inspirations for the development and utilization of flavonoids from sea buckthorn (*Hippophae rhamnoides* L.) both in the pharmaceutical and food industries.

2. Methodology of Research

A literature-based search was conducted to provide an overview of extraction, structure, detection, bioactivity, and metabolism of flavonoids from sea buckthorn (*Hippophae rhamnoides* L.), using accessible online databases such as SciFinder, PubMed, SpringerLink, Baidu Academic, Google Scholar, ScienceDirect, American Chemical Society (ACS) publications, Web of Science, and China Knowledge Resource Integrated Databases (CNKI). The literature survey was performed using different keywords including sea buckthorn (*Hippophae rhamnoides* L.), flavonoids, extraction, structure, detection, bioactivity, and metabolism, which resulted in the gathering of many references. The plant name was confirmed from the websites of "World Flora Online" and "The Plant List." All chemical structures were drawn with ChemDraw by the authors. Some key abbreviations of this review are listed in Table 1.

Table 1: Some key abbreviations of this paper.

Abbreviations	
ACS	American Chemical Society
ALT	Alanine aminotransferase
AMP	5′-Monophosphate
CNKI	China Knowledge Resource Integrated Databases
COX-2	Cyclooxygenase-2
GOT	Glutamic oxaloacetic transaminase
HPLC	High-performance liquid chromatography
IL-1β	Interleukin-1β
IL-4	Interleukin-4
IL-13	Interleukin-13
IRS-1	Insulin receptor substrate-1
ISG	Interferon stimulated gene
LPS	Lipopolysaccharide
MAPK	Mitogen-activated protein kinase
MCE	Mitotic clone expansion
MS	Mass spectrometry
NFkB	Nuclear factor-k-gene binding
NMR	Nuclear magnetic resonance
NO	Nitric oxide
PAR-2	Protease activated receptor-2
PKB	Protein kinase B
PPAR-α	Peroxisome proliferator-activated receptor-α
PPAR-γ	Peroxisome proliferator-activated receptor-γ
PTP-1B	Protein tyrosine phosphatase-1B
TAK-1	TGF-activated kinase-1
TGF-β	Transforming growth factor-β
TNF-α	Tumor necrosis factor-α
UV	Ultraviolet spectrophotometry

3. Extraction Methods of Flavonoids

3.1. Solvent Extraction Method. The solvent extraction process was based on the principle of similar dissolution, considering the solubility and food safety of sea buckthorn flavonoids, and selecting the appropriate solvent to achieve dissolution extraction. Solvent extraction was the most basic extraction technology of flavonoids from sea buckthorn (Figure 1). Till now, the different concentrations of water or ethanol were generally used as the extractant. Prof. Shulin Wang studied the technology of reflux extraction of flavonoids from sea buckthorn leaves with water as solvent. The optimal technological conditions were optimized by orthogonal test: extraction temperature of 90°C, ratio of material to liquid of 1 : 10 (g/mL), extraction time of 2 h, and filter residue extraction of 1 : 8 (g/mL) for 1.5 h. Under this technological condition, the extraction rate of flavonoids from sea buckthorn was 0.93% [10]. Flavonoids were extracted by 75% ethanol heating and refluxing from sea buckthorn (*Hippophae rhamnoides* L.). The optimum technological conditions were as follows: ratio of material to liquid of 1 : 16 (g/mL) and reflux time of 6 h. The extraction rate of flavonoids from sea buckthorn (*Hippophae rhamnoides* L.) reached 19.19% [11]. Hui et al. studied the flavonoids of sea buckthorn by using the ethanol reflux extraction process. Based on the previous single factor test results, the optimal process conditions were optimized by orthogonal design test: 70% ethanol as the extraction solvent, ratio of material to liquid of 1 : 16 (g/mL), extraction time of 2.0 h, and extraction times of 3. Under this process condition, the flavonoid extraction rate of sea buckthorn was 5.64% [12]. In addition, Li et al. studied the ethanol extraction process of flavonoids from sea buckthorn. The optimal extraction conditions of flavonoids from sea buckthorn were as follows: ethanol concentration of 60%, material to liquid ratio of 1 : 20 (g/mL), extraction temperature of 80°C, extraction time of 30 min, and the extraction rate of flavonoids from sea buckthorn of 0.14% [13]. The solvent extraction method is simple in equipment, convenient in operation, and low in cost, but it has many problems, such as long time consumption, large loss of material and liquid, low extraction efficiency, and poor purity of flavonoids.

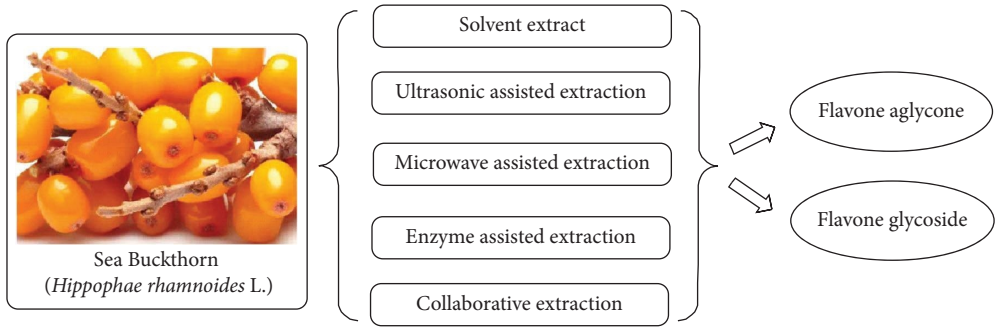


Figure 1: The extraction methods of flavonoids from sea buckthorn (*Hippophae rhamnoides* L.). Note: five extraction methods were reported to obtain flavonoids from sea buckthorn (*Hippophae rhamnoides* L.), and these flavonoids were divided into flavone aglycones and flavone glycosides.

3.2. Ultrasound-Assisted Extraction Method. Ultrasound-assisted extraction had strong penetrability and good directivity, as well as cavitation and thermal effects produced by ultrasonic radiation, which quickly destroyed the integrity of cell wall, improved the permeability of cell wall, helped the solvent quickly penetrate into cells, and released cell contents (Figure 1). In this way, the effective ingredients were rapidly dissolved, which improved the extraction efficiency [14]. Ultrasound-assisted ethanol extraction of flavonoids from sea buckthorn was used on the basis of single factor experiment. The optimum technological conditions were as follows: 40% ethanol concentration, ultrasonic frequency of 20 kHz, extraction at room temperature for 15 min, and extraction rate of flavonoids from sea buckthorn of 5.03% [15]. Based on ultrasound-assisted ethanol extraction of flavonoids from sea buckthorn (*Hippophae rhamnoides* L.), the extraction conditions were optimized by response surface methodology as follows: 70.64% ethanol, ultrasonic power of 561.50 W, material to liquid ratio of 1 : 35 (g/mL), and ultrasonic time of 30 min. Under this technological condition, the extraction rate of flavonoids from sea buckthorn was 10.51 mg/g [16]. Jin et al. took ethanol and hydrochloric acid solution as the extracting agents, and the optimal extraction conditions were determined as follows: 50% ethanol, hydrochloric acid concentration of 3 mol/L, material to liquid ratio of 1 : 20 (g/mL), ultrasonic power of 80 W, ultrasonic time of 30 min, and flavonoid extraction rate of flavonoids from sea buckthorn of 6.34% [17]. Ultrasound-assisted extraction of flavonoids from sea buckthorn (*Hippophae rhamnoides* L.) had the advantages of low extraction temperature, less time, solvent saving, less impurity content, and high extraction rate. However, the one-time investment cost of the required equipment was high, and there was environmental pollution caused by ultrasonic noise. So far, it was only limited to laboratory research, and it was not yet possible to achieve industrial production.

3.3. Microwave-Assisted Extraction Method. Flavonoids were extracted from sea buckthorn by microwave-assisted extraction method. Its working principle was based on microwave penetrating medium and cells and increasing temperature and pressure inside the cells. As a result, it caused the rupture of the cell wall of sea buckthorn (Figure 1). As a result, this method promoted the release of flavonoids inside the cells into the solvent as soon as possible and improved the extraction rate of flavonoids [18]. Fan et al. studied the flavonoids of sea buckthorn (*Hippophae rhamnoides* L.) by using the microwave-assisted ethanol extraction based on single factor analysis and orthogonal design test. The optimal technological conditions were determined as follows: 50% ethanol as the extracting agent, ratio of material to liquid of 1 : 40 (g/mL), microwave power of 550 W, microwave time of 5 min, and flavonoid extraction rate of 0.19% [19]. Zhang et al. studied the microwave-assisted extraction process of flavonoids from sea buckthorn (*Hippophae rhamnoides* L.) through orthogonal design test. The optimal extraction process was optimized: 60% ethanol concentration, pH = 10, material to liquid ratio of 1 : 20 (g/mL), microwave time of 3 min, and flavonoid extraction rate of 2.02% [20]. Microwave-assisted extraction had many advantages, such as convenient processing, significantly reducing extraction time, and effectively reducing economic and environmental costs. However, due to the relatively backward research and development of microwave extraction equipment suitable for industrial production, the research on microwave-assisted extraction of flavonoids from sea buckthorn was only carried out in the laboratory, which was still a certain distance from the realization of industrial production.

3.4. Enzyme-Assisted Extraction Method. Enzymatic assisted extraction of flavonoids from sea buckthorn was to use enzymes to degrade cellulose and hemicellulose in the cell wall of sea buckthorn (Figure 1). This method destroyed dense structure and tissue, improved the permeability, and reduced the mass transfer resistance of solvent and flavonoids in the extraction process. It facilitated the dissolution of flavonoids from the cell and achieved effective extraction [21]. The high specificity and variability of the enzyme determined that the efficiency of enzyme-assisted extraction of sea buckthorn flavonoids was closely related to the type of enzyme, solvent, pH, and temperature. Zhu et al. studied the flavonoids from sea buckthorn by using cellulase-assisted extraction technology and found the optimum extraction conditions based on orthogonal design test: 4% cellulase addition, material to liquid ratio of 1 : 50 (g/mL),

temperature of 40°C, and extraction time of 2 h. The results showed that the order of factors affecting the extraction rate was as follows: enzyme dosage > enzymolysis time > material to liquid ratio > enzymolysis temperature [22]. Enzyme-assisted extraction had the advantages of mild extraction conditions, high extraction rate, and protection of flavonoid activity. Thus, it was widely used in the extraction of many other active components of natural products.

3.5. Collaborative Extraction Method. Comprehensive utilization of several extraction methods to cooperatively assisted extraction of active components from natural products realized the complementary advantages of several methods and improved the extraction rate of active components. This process was a new auxiliary extraction technology developed in past years (Figure 1). The best extraction conditions of flavonoids from sea buckthorn (*Hippophae rhamnoides* L.) were determined as follows: ratio of material to liquid of 1 : 70 (g/mL), addition amount of sucrose ester of 0.02 g/mL, temperature of 70°C, and extraction time of 1.5 h. Under this technological condition, the extraction rate of flavonoids from sea buckthorn was 1.60% [23]. Prof. Furong Zhao used ultrasound-microwave-assisted extraction of flavonoids from sea buckthorn and found the optimal process conditions optimized by response surface methodology: 68.10% ethanol, fixed ultrasonic temperature of 60°C, ultrasonic time of 25 min, material to liquid ratio of 1 : 17 (g/mL), and flavonoid extraction rate of sea buckthorn of 4.28%. Compared with ethanol reflux, microwave-assisted extraction, and ultrasound-assisted extraction, the flavonoid extraction rate of sea buckthorn increased by 14.67%, 24.04%, and 36.63%, respectively [24]. Compared with solvent extraction method, synergistic extraction had the advantages of less solvent consumption, shorter extraction time, and significantly improving the extraction rate of flavonoids. However, several methods of synergistic assisted extraction had relatively complex process conditions and higher requirements for equipment.

4. Flavonoids

Previous phytochemical research studies exhibited that flavonoids were the main chemical components in sea buckthorn (*Hippophae rhamnoides* L.), which had been discovered in fruits, leaves, branches, roots, and seeds of sea buckthorn (*Hippophae rhamnoides* L.). Till now, a total of 99 flavonoids were isolated and identified from sea buckthorn (*Hippophae rhamnoides* L.), including flavone aglycones and flavone glycosides.

4.1. Flavone Aglycones. So far, a total of 18 flavone aglycones were isolated from different parts of sea buckthorn (*Hippophae rhamnoides* L.), which included the types of flavonols (**1**-**2**, **5**, and **7**–**9**), 3-methoxyflavonoids (**3**-**4**), flavonoid (**6**), dihydroflavonoid (**10**), and catechins (**11**–**18**). Analyzing the structures of above compounds, it was found that the positions of C-5/7 were often substituted by two hydroxyl groups except for compound (**4**), and the positions of C-3′/4′ were often replaced by hydroxyl or methoxy groups. The related information of flavonoid aglycones (**1**–**18**) is shown in Table 2.

4.2. Flavone Glycosides. Up to now, a total of 81 flavone glycosides were isolated from sea buckthorn (*Hippophae rhamnoides* L.). These compounds mainly took isorhamnetin, quercetin, and kaempferol as aglycones, which combined with glucose, rhamnose, arabinose, and rutin to form different flavone glycosides [25]. According to the structural characteristics of these compounds, interestingly, the positions of C-3/5/7 were often substituted by pentoside, glucoside, rutinoside, galactoside, hexoside, neohesperidoside, rhamnoside, and arabinoside of compounds (**19**–**99**). In these flavonoid glycosides, most of the compounds belong to flavonoid polyglycosides. In particular, the proportion of diglycosides is the largest of above compounds. The details of these compounds (**19**–**99**) are shown in Table 3.

5. Detection Methods of Flavonoids

The detection methods of flavonoids from sea buckthorn included ultraviolet spectrophotometry (UV), high-performance liquid chromatography (HPLC), high-performance liquid chromatography-mass spectrometry (HPLC-MS), and nuclear magnetic resonance (NMR). The representative substances and detection methods of sea buckthorn (*Hippophae rhamnoides* L.) are shown in Table 4.

5.1. UV Detection Method. The determination principle of UV was that flavonoids included cinnamoyl generated absorption bands at 300–550 nm and benzoyl generated absorption bands at 240–280 nm in the ultraviolet spectrum. The concentration of the target substance was calculated quantitatively by measuring the absorbance of the solution in the spectral area [45]. This method had high sensitivity and good repeatability and was suitable for determining the content of total flavonoids in sea buckthorn (*Hippophae rhamnoides* L.).

5.2. HPLC Detection Method. HPLC and HPLC-MS had the advantages of less interference, good reproducibility, fast analysis speed, and high sensitivity, which were more suitable for the structural determination of flavonoids from sea buckthorn (*Hippophae rhamnoides* L.). The determination of flavonoids in sea buckthorn (*Hippophae rhamnoides* L.) by HPLC mainly focused on the detection of rutin and isorhamnetin, but it did not reflect all flavonoids in sea buckthorn (*Hippophae rhamnoides* L.), which greatly restricted the research on the pharmaceutical mechanism of sea buckthorn (*Hippophae rhamnoides* L.) flavonoids [46]. However, HPLC-MS quickly and accurately conducted quantitative analysis of substances, which was conducive to the discovery of target trace components in the sea buckthorn (*Hippophae rhamnoides* L.).

Table 2: The flavonoids (**1–18**) were isolated from sea buckthorn (*Hippophae rhamnoides* L.).

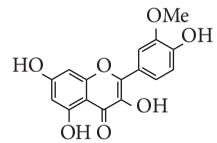
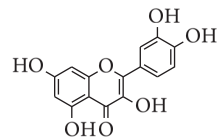
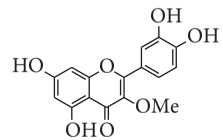
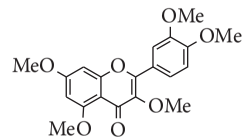
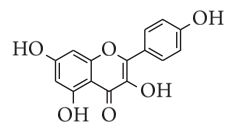
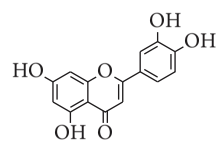
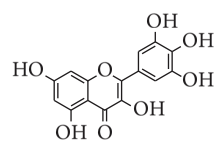
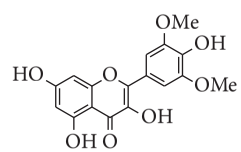
No	Name	Structure	Formula	Part	Reference
1	Isorhamnetin		$C_{16}H_{12}O_7$	Fruit, leaf, root, seed	Liu et al. [25]
2	Quercetin		$C_{15}H_{10}O_7$	Fruit, leaf, root, seed	Hiroshige et al. [26]
3	Quercetin-3-methylether		$C_{16}H_{12}O_7$	Fruit	Pop et al. [27]
4	Pentamethylquercetin		$C_{20}H_{20}O_7$	Root	Hiroshige et al. [26]
5	Kaempferol		$C_{15}H_{10}O_6$	Fruit, leaf, root, seed	Hiroshige et al. [26]
6	Luteolin		$C_{15}H_{10}O_6$	Fruit, leaf, seed	Cai et al. [28]
7	Myricetin		$C_{15}H_{10}O_8$	Leaf, root, seed	Yang et al. [29]
8	Syringetin		$C_{17}H_{14}O_8$	Root	Hiroshige et al. [26]

Table 2: Continued.

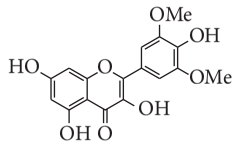
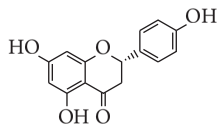
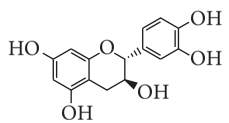
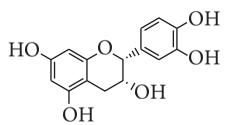
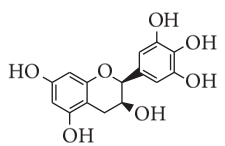
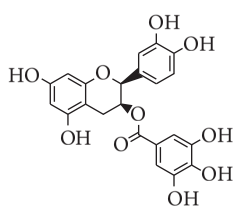
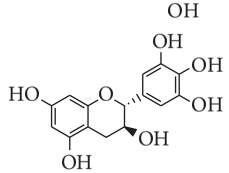
No	Name	Structure	Formula	Part	Reference
9	Tamarixetin-3-O-glucose		$C_{22}H_{22}O_{12}$	Fruit	Ji et al. [30]
10	Naringenin		$C_{15}H_{12}O_5$	Fruit	Hiroshige et al. [26]
11	(+)-Catechin		$C_{15}H_{14}O_6$	Fruit, branch	Yasukawa et al. [31]
12	(-)-Epicatechin		$C_{15}H_{14}O_6$	Fruit, leaf	Hiroshige et al. [26]
13	(-)-Epigallocatechin		$C_{15}H_{14}O_7$	Fruit, leaf, seed, branch	Yasukawa et al. [31]
14	(-)-Epicatechin gallate		$C_{22}H_{18}O_{10}$	Fruit, leaf	Liu et al. [25]
15	(+)-Gallocatechin		$C_{15}H_{14}O_7$	Fruit, leaf, branch	Hiroshige et al. [26]

Table 2: Continued.

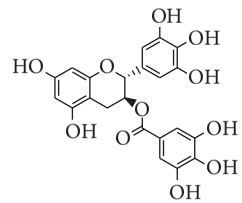
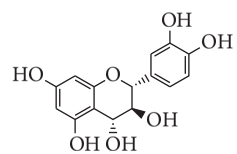
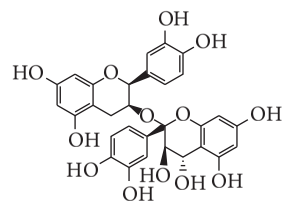
No	Name	Structure	Formula	Part	Reference
16	(+)-Gallocatechin gallate		$C_{22}H_{18}O_{11}$	Fruit, leaf	Hiroshige et al. [26]
17	Leucocyanidin		$C_{15}H_{14}O_7$	Fruit, leaf	Lu et al. [32]
18	Proanthocyanidin		$C_{30}H_{26}O_{13}$	Fruit	Teleszko et al. [33]

Table 3: The flavonoids (**19–99**) were isolated from sea buckthorn (*Hippophae rhamnoides* L.).

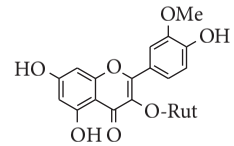
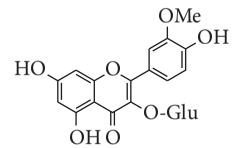
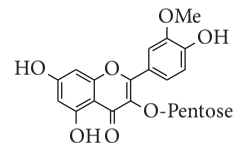
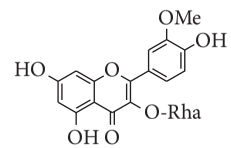
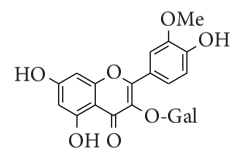
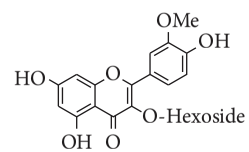
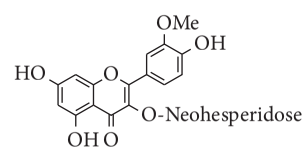
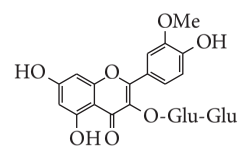
No	Name	Structure	Formula	Part	Reference
19	Isorhamnetin-3-O-rutinoside		$C_{28}H_{32}O_{16}$	Fruit, leaf	Pop et al. [27]
20	Isorhamnetin-3-O-glucoside		$C_{22}H_{\backslash 22}O_{12}$	Fruit, leaf	Pop et al. [27]
21	Isorhamnetin-3-O-pentoside		$C_{21}H_{20}O_{11}$	Fruit	Tkacz et al. [8]
22	Isorhamnetin-3-O-rhamnoside		$C_{21}H_{18}O_{12}$	Fruit, leaf	Hiroshige et al. [26]
23	Isorhamnetin-3-O-galactoside		$C_{22}H_{22}O_{12}$	Fruit	Suryakumar and Gupta [34]
24	Isorhamnetin-3-O-hexoside		$C_{22}H_{22}O_{12}$	Fruit, leaf	Suryakumar and Gupta [34]
25	Isorhamnetin-3-O-neohesperidoside		$C_{28}H_{32}O_{16}$	Fruit, leaf	Suryakumar and Gupta [34]
26	Isorhamnetin-3-O-glucoglucoside		$C_{28}H_{32}O_{17}$	Fruit	Suryakumar and Gupta [34]

Table 3: Continued.

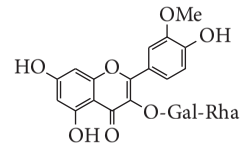
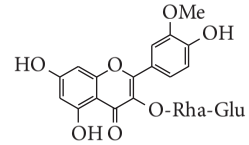
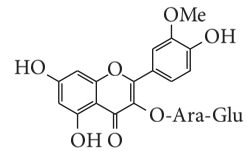
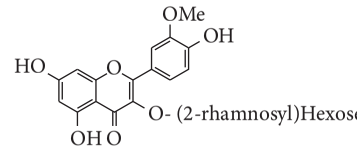
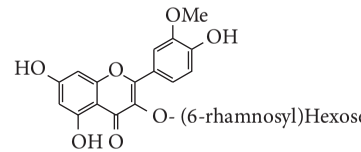
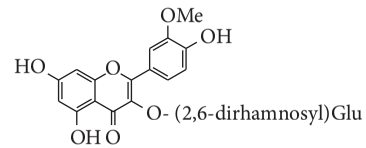
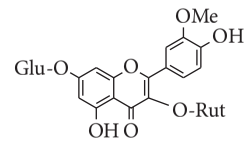
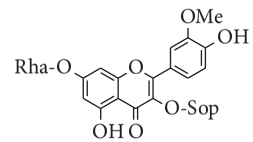
No	Name	Structure	Formula	Part	Reference
27	Isorhamnetin-3-O-galactorhamnoside		$C_{28}H_{32}O_{16}$	Fruit	Suryakumar and Gupta [34]
28	Isorhamnetin-3-O-rhamnosylglucoside		$C_{28}H_{32}O_{16}$	Fruit, leaf	Pop et al. [27]
29	Isorhamnetin-3-O-α-L-arabinose-(1⟶4)-β-D-glucoside		$C_{27}H_{30}O_{16}$	Fruit	Ji et al. [30]
30	Isorhamnetin-3-O-(2-rhamnosyl)hexoside		$C_{28}H_{32}O_{16}$	Fruit	Tkacz et al. [8]
31	Isorhamnetin-3-O-(6-rhamnosyl)hexoside		$C_{28}H_{32}O_{16}$	Fruit	Tkacz et al. [8]
32	Isorhamnetin-3-O-(2,6-dirhamnosyl)glucoside		$C_{34}H_{42}O_{20}$	Fruit	Tkacz et al. [8]
33	Isorhamnetin-3-O-rutinoside-7-O-glucoside		$C_{34}H_{42}O_{21}$	Fruit, leaf	Suryakumar and Gupta [34]
34	Isorhamnetin-3-O-sophoroside-7-O-rhamnoside		$C_{34}H_{42}O_{21}$	Fruit, leaf	Pop et al. [27]

Table 3: Continued.

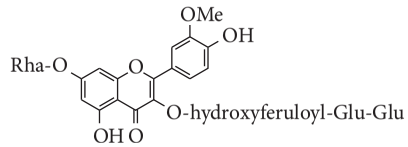
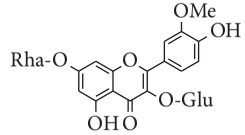
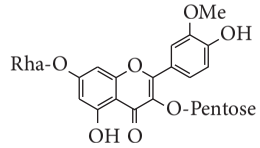
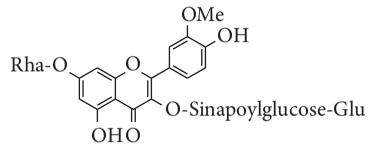
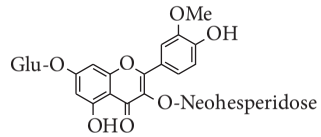
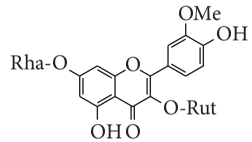
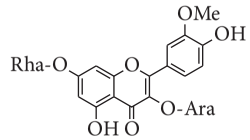
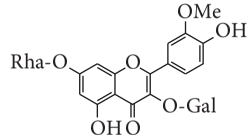
No	Name	Structure	Formula	Part	Reference
35	Isorhamnetin-3-O-hydroxyferuloyl-glucosylglucoside-7-O-rhamnoside		$C_{44}H_{50}O_{25}$	Fruit	Tkacz et al. [8]
36	Isorhamnetin-3-O-glucoside-7-O-rhamnoside		$C_{28}H_{32}O_{16}$	Fruit, leaf	Pop et al. [27]
37	Isorhamnetin-3-O-pentoside-7-O-rhamnoside		$C_{27}H_{30}O_{15}$	Fruit	Tkacz et al. [8]
38	Isorhamnetin-3-O-sinapoylglucose-glucoside-7-O-rhamnoside		$C_{45}H_{52}O_{25}$	Fruit, leaf	Pop et al. [27]
39	Isorhamnetin-3-O-neohesperidoside-7-O-glucoside		$C_{34}H_{42}O_{21}$	Leaf	Pop et al. [27]
40	Isorhamnetin-3-O-rutinoside-7-O-rhamnoside		$C_{34}H_{42}O_{21}$	Fruit	Tkacz et al. [8]
41	Isorhamnetin-3-O-arabinoside-7-O-rhamnoside		$C_{27}H_{30}O_{15}$	Leaf	Qin et al. [35]
42	Isorhamnetin-3-O-galactoside-7-O-rhamnoside		$C_{28}H_{32}O_{16}$	Leaf	Ji et al. [30]

Table 3: Continued.

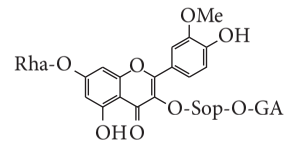
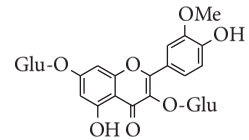
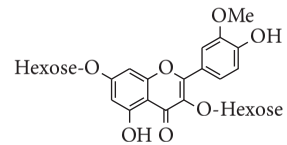
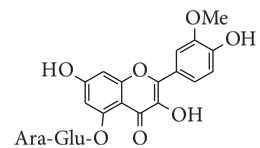
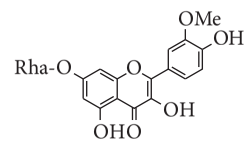
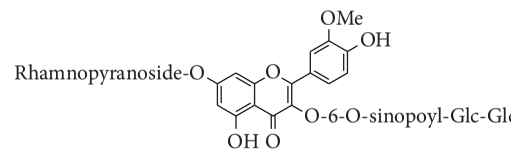
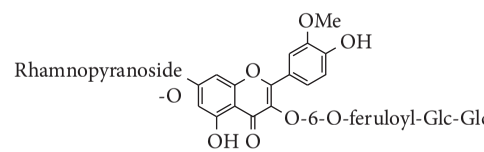
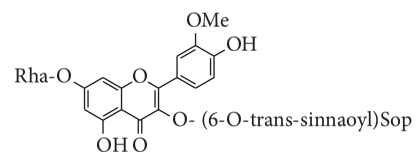
No	Name	Structure	Formula	Part	Reference
43	Isorhamnetin-3-O-sophoroside-O-glucuronic acid-7-O-rhamnoside		$C_{40}H_{50}O_{27}$	Leaf	Qin et al. [35]
44	Isorhamnetin-3,7-O-diglucoside		$C_{28}H_{32}O_{17}$	Fruit	Teleszko et al. [33]
45	Isorhamnetin-3,7-O-dihexoside		$C_{28}H_{32}O_{17}$	Fruit, leaf	Pop et al. [27]
46	Isorhamnetin-5-O-glucoarabinoside		$C_{27}H_{30}O_{16}$	Fruit	Suryakumar and Gupta [34]
47	Isorhamnetin-7-O-rhamnoside		$C_{21}H_{18}O_{12}$	Fruit	Suryakumar and Gupta [34]
48	Isorhamnetin-3-O-(6-O-*E*-sinapoyl-*β*-D-glucopyranosyl)-(1⟶2)-*β*-D-glucopyranoside-7-O-*α*-L-rhamnopyranoside		$C_{45}H_{52}O_{25}$	Fruit	Fang et al. [36]
49	Isorhamnetin-3-O-(6-O-*E*-feruloyl-*β*-D-glucopyranosyl)-(1⟶2)-*β*-D-glucopyranoside-7-O-*α*-L-rhamnopyranoside		$C_{44}H_{50}O_{24}$	Fruit	Fang et al. [36]
50	Isorhamnetin -3-O- (6-O-*trans*-sinnapoyl) sophoroside-7-O-*α*-L-rhamnoside		$C_{45}H_{52}O_{25}$	Fruit	Upadhyay et al. [37]

Table 3: Continued.

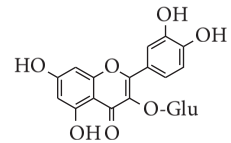
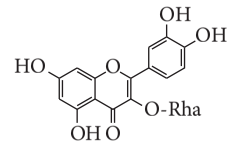
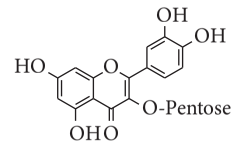
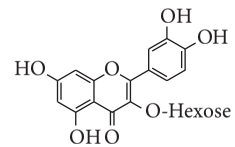
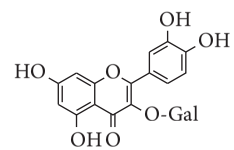
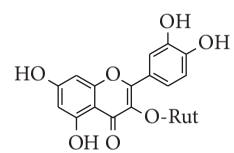
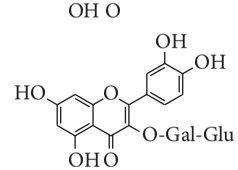
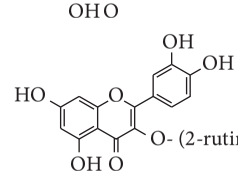
No	Name	Structure	Formula	Part	Reference
51	Quercetin-3-O-glucoside		$C_{21}H_{20}O_{12}$	Fruit, leaf	Hiroshige et al. [26]
52	Quercetin-3-O-rhamnoside		$C_{21}H_{20}O_{11}$	Fruit	Hiroshige et al. [26]
53	Quercetin-3-O-pentoside		$C_{20}H_{18}O_{11}$	Leaf	Pop et al. [27]
54	Quercetin-3-O-hexoside		$C_{21}H_{20}O_{12}$	Fruit, leaf	Pop et al. [27]
55	Quercetin-3-O- galactoside		$C_{21}H_{20}O_{11}$	Leaf	Chen et al. [38]
56	Quercetin-3-O-rutinoside		$C_{27}H_{30}O_{16}$	Fruit	Teleszko et al. [33]
57	Quercetin-3-O-galactoglucoside		$C_{27}H_{30}O_{17}$	Leaf	Ji et al. [30]
58	Quercetin-3-O-(2-rutinosyl)glucoside		$C_{33}H_{40}O_{21}$	Fruit, leaf	Suryakumar and Gupta [34]

Table 3: Continued.

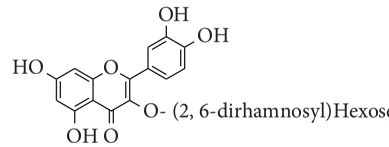
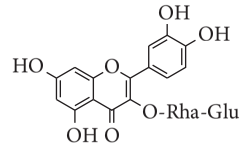
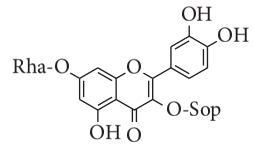
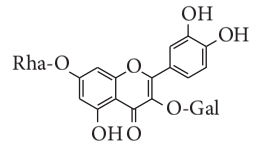
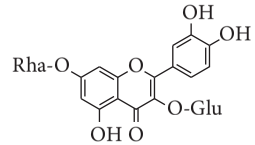
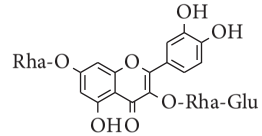
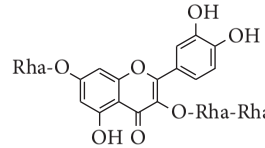
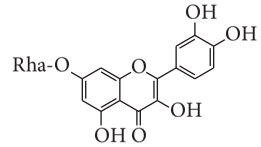
No	Name	Structure	Formula	Part	Reference
59	Quercetin-3-O-(2,6-dirhamnosyl)hexoside		$C_{33}H_{40}O_{20}$	Fruit	Tkacz et al. [8]
60	Quercetin-3-O-rhamnosylglucoside		$C_{27}H_{30}O_{16}$	Fruit, leaf	Pop et al. [27]
61	Quercetin-3-O-sophoroside-7-O-rhamnoside		$C_{33}H_{40}O_{21}$	Fruit, leaf	Pop et al. [27]
62	Quercetin-3-O-galactoside-7-O-rhamnoside		$C_{27}H_{30}O_{16}$	Fruit	Tkacz et al. [8]
63	Quercetin-3-O-glucoside-7-O-rhamnoside		$C_{27}H_{30}O_{16}$	Fruit, leaf	Pop et al. [27]
64	Quercetin-3-O-rhamnosylglucoside-7-O-rhamnoside		$C_{33}H_{40}O_{20}$	Leaf	Qin et al. [35]
65	Quercetin-3-O-rhamnosylrhamnoside-7-O-glucoside		$C_{33}H_{40}O_{20}$	Leaf	Qin et al. [35]
66	Quercetin-7-O-rhamnoside		$C_{21}H_{20}O_{11}$	Fruit	Suryakumar and Gupta [34]

Table 3: Continued.

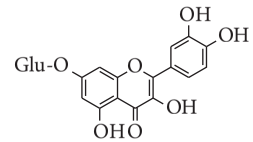
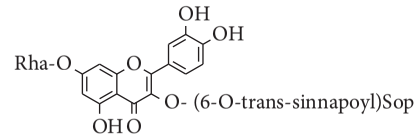
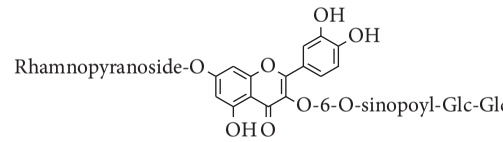
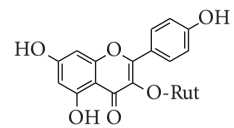
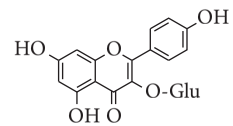
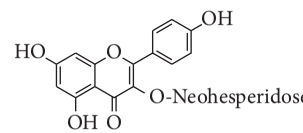
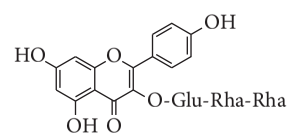
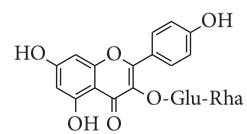
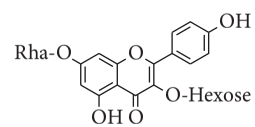
No	Name	Structure	Formula	Part	Reference
67	Quercetin-7-O-glucoside		$C_{21}H_{20}O_{12}$	Leaf	Qin et al. [35]
68	Quercetin-3-O-(6-O-*trans*-sinnapoyl)sophoroside-7-O-α-L-rhamnoside		$C_{44}H_{50}O_{25}$	Fruit	Chen et al. [38]
69	Quercetin-3-O-(6-O-*E*-sinapoyl-β-D-glucopyranosyl)-(1⟶2)-β-D-glucopyranoside-7-O-α-L-rhamnopyranoside		$C_{44}H_{50}O_{25}$	Fruit	Chen et al. [39]
70	Kaempferol-3-O-rutinoside		$C_{27}H_{30}O_{15}$	Fruit, leaf	Pop et al. [27]
71	Kaempferol-3-O-glucoside		$C_{21}H_{20}O_{11}$	Leaf	Hiroshige et al. [26]
72	Kaempferol-3-O-neohesperidoside		$C_{27}H_{30}O_{15}$	Leaf	Pop et al. [27]
73	Kaempferol-3-O-β-D-glucose-(1⟶2)-α-L-rhamnose-(1⟶2)-α-L-rhamnoside		$C_{33}H_{40}O_{19}$	Fruit	Ji et al. [30]
74	Kaempferol-3-O-β-D-glucose-(1⟶2)-β-D-rhamnoside		$C_{27}H_{30}O_{15}$	Leaf	Qin et al. [35]
75	Kaempferol-3-O-hexoside-7-O-rhamnoside		$C_{27}H_{30}O_{15}$	Fruit	Tkacz et al. [8]

Table 3: Continued.

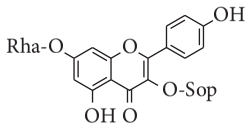
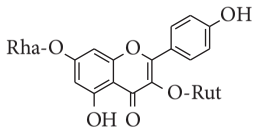
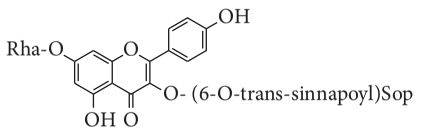
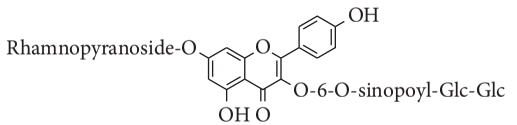
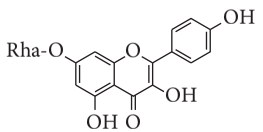
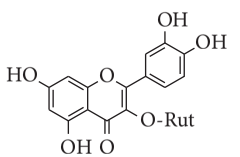
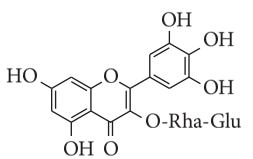
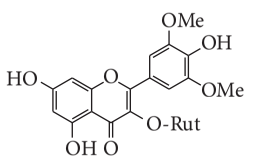
No	Name	Structure	Formula	Part	Reference
76	Kaempferol-3-O-sophoroside-7-O-rhamnoside		$C_{33}H_{40}O_{21}$	Fruit	Chen et al. [38]
77	Kaempferol-3-O-rutinoside-7-O-rhamnoside		$C_{33}H_{40}O_{19}$	Leaf	Qin et al. [35]
78	Kaempferol-3-O-(6-O-*trans*-sinnapoyl)sophoroside-7-O-*α*-L-rhamnoside		$C_{44}H_{50}O_{24}$	Fruit	Chen et al. [38]
79	Kaempferol-3-O-(6-O-*E*-sinapoyl-*β*-D-glucopyranosyl)-(1⟶2)-*β*-D-glucopyranoside-7-O-*α*-L-rhamnopyranoside		$C_{44}H_{50}O_{24}$	Fruit	Chen et al. [39]
80	Kaempferol-7-O-rhamnoside		$C_{21}H_{20}O_{10}$	Fruit	Chen et al. [38]
81	Rutin		$C_{27}H_{30}O_{16}$	Fruit, leaf, seed	Pop et al. [27]
82	Myricetin-3-O-*α*-L-rhamnose-(1⟶6)-*β*-D-glucoside		$C_{27}H_{30}O_{17}$	Leaf	Qin et al. [35]
83	Syringetin-3-O-rutinoside		$C_{29}H_{34}O1_7$	Fruit	Chen et al. [38]

Table 3: Continued.

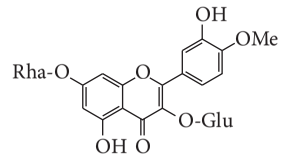
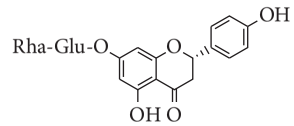
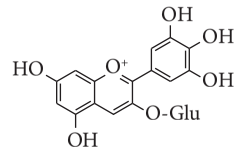
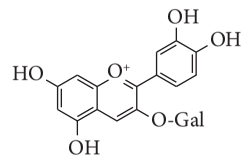
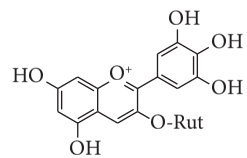
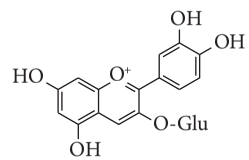
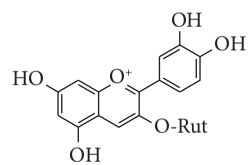
No	Name	Structure	Formula	Part	Reference
84	Tamarixetin-3-O-glucoside-7-O-rhamnoside		$C_{26}H_{32}O_{16}$	Fruit	Ji et al. [30]
85	Naringin		$C_{27}H_{32}O_{14}$	Fruit, leaf, seed	Cai et al. [28]
86	Delphinidin-3-glucoside		$C_{21}H_{21}O_{12}$	Fruit	Na et al. [40]
87	Cyanidin-3-galactoside		$C_{21}H_{21}O_{12}$	Fruit	Hosseinian and Beta [41]
88	Delphinidin-3-rutinoside		$C_{28}H_{33}O_{15}$	Fruit	Hosseinian and Beta [41]
89	Cyanidin-3-glucoside		$C_{21}H_{21}O_{11}$	Fruit	Hosseinian and Beta [41]
90	Cyanidin-3-rutinoside		$C_{27}H_{31}O_{15}$	Fruit	Hosseinian and Beta [41]

Table 3: Continued.

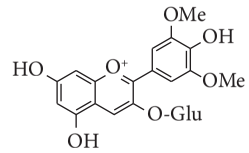
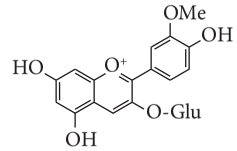
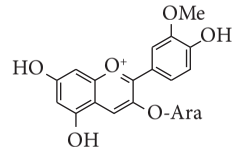
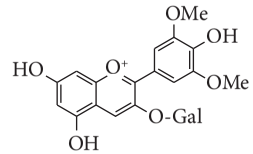
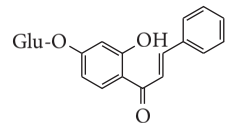
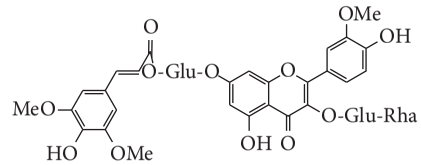
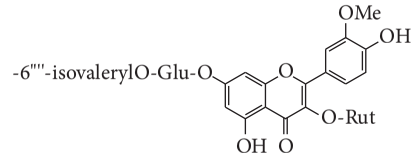
No	Name	Structure	Formula	Part	Reference
91	Malvidin-3-glucoside		$C_{23}H_{25}O_{12}$	Fruit	Hosseinian and Beta [41]
92	Peonidin-3-glucoside		$C_{22}H_{23}O_{11}$	Fruit	Hosseinian and Beta [41]
93	Peonidin-3-arabinoside		$C_{21}H_{21}O_{10}$	Fruit	Hosseinian and Beta [41]
94	Malvidin-3-galactoside		$C_{23}H_{25}O_{12}$	Fruit	Hosseinian and Beta [41]
95	2,4-Dilhydroxy-chalcones-2-O-glucoside		$C_{21}H_{23}O_8$	Fruit	Suryakumar and Gupta [34]
96	Isorhamnetin-3-O-α-L-rhamnosyl-(1⟶6)-β-D-glucosyl-7-O-(6-O-sinapinyl)-β-D-glucoside		$C_{45}H_{52}O_{25}$	Juice	Na et al. [40]
97	Isorhamnetin-3-O-rutinosyl-7-O-β-(6‴″-isovaleryl)-glucoside		$C_{39}H_{49}O_{22}$	Juice	Na et al. [40]

Table 3: Continued.

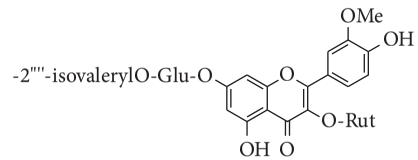
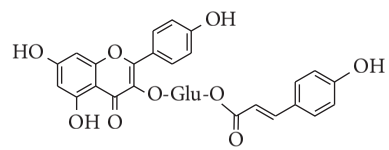
No	Name	Structure	Formula	Part	Reference
98	Isorhamnetin-3-O-rutinosyl-7-O-β-(2‴″-isovaleryl)-glucoside		$C_{39}H_{50}O_{22}$	Juice	Na et al. [40]
99	Tiliroside		$C_{30}H_{26}O_{13}$	Juice	Na et al. [40]

Table 4: Structures and detection methods of representative substances of flavonoids from sea buckthorn (*Hippophae rhamnoides* L.).

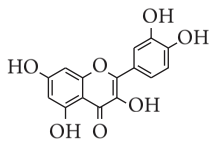
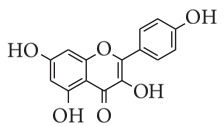
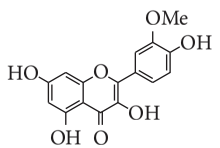
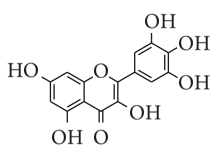
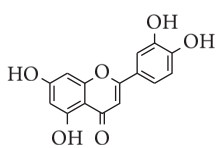
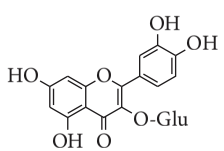
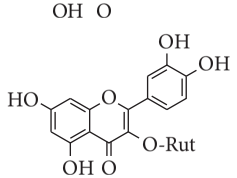
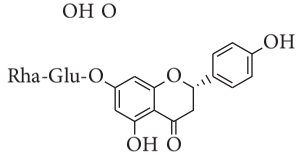
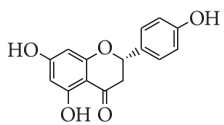
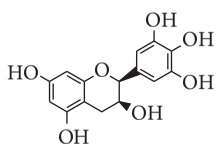
No	Name	Structure	Detection methods	Secondary mass spectrometry ion	Reference
1	Quercetin		HPLC, HPLC-MS	Parent ion (m/z: 308.80), daughter ion (m/z: 151.0)	Li et al. [42]
2	Kaempferol		HPLC, HPLC-MS	Parent ion (m/z: 284.8), daughter ion (m/z: 150.8)	Li et al. [42]
3	Isorhamnetin		HPLC, HPLC-MS	Parent ion (m/z: 315.0), daughter ion (m/z: 300.1)	Kumar et al. [43]
4	Myricetin		HPLC-MS	Parent ion(m/z: 316.9), daughter ion(m/z: 137.0)	Kumar et al. [43]
5	Luteolin		HPLC-MS	Parent ion (m/z: 284.7), daughter ion (m/z: 135.8)	Cai et al. [44]
6	Quercetin-3-O-glucoside		HPLC-MS	Parent ion (m/z: 463.1), daughter ion (m/z: 301.0)	Cai et al. [44]
7	Rutin		HPLC, HPLC-MS	Parent ion (m/z: 609.0), daughter ion (m/z: 207.9)	Li et al. [42]
8	Naringin		HPLC-MS	Parent ion (m/z: 579.5), daughter ion (m/z: 116.0)	Cai et al. [28]

Table 4: Continued.

No	Name	Structure	Detection methods	Secondary mass spectrometry ion	Reference
9	Naringenin		HPLC-MS	Parent ion (m/z:271.0), daughter ion (m/z: 119.0)	Cai et al. [44]
10	(-)-epigallocatechin		HPLC-MS	Parent ion (m/z: 442.3), daughter ion (m/z: 289.2)	Cai et al. [44]

5.3. NMR Detection Method. NMR has become an important method for structural analysis of flavonoids in recent years. Anhydrous deuterium had a wide dissolution range and high resolution of proton signal peaks, which was an ideal solvent for identifying phenolic hydroxyl groups on the parent nucleus of flavonoids [47]. Therefore, anhydrous deuterium was often used as a solvent in NMR instead of dimethyl sulfoxide. The NMR method was accurate, reproducible, simple, and easy to operate. It also saved a lot of reagents and had little pollution, which was a potential method for determination of flavonoids from sea buckthorn (*Hippophae rhamnoides* L.). However, there were few literature reports on the determination of *H. rhamnoides* flavonoids by the NMR method, and the research of NMR detection method should be strengthened.

6. Bioactive Flavonoids

Modern medical research showed that flavonoids were metabolized into small molecule monophenolic acid and other metabolites by intestinal microorganisms after being ingested by human body [48]. These metabolites combined with specific receptors on the surface of body tissue cells and affected the expression of multiple genes and their signal pathways [49]. A large number of studies had shown that flavonoids played a variety of physiological activities by regulating intestinal flora, which prevented a variety of diseases [50]. Many studies had proved that the flavonoids from sea buckthorn (*Hippophae rhamnoides* L.) possessed antiviral, anti-inflammatory, hepatoprotective, weight-reducing, and hypoglycemic activities and had regulatory effects on intestinal microorganisms through cell models, animal models, and other methods, but the relevant mechanisms were not clear which needed to be further explored (Figure 2).

6.1. Antiviral. Among secondary metabolites, flavonoids played an important role in enhancing the medicinal properties of human and animal diseases. The previous study found that flavonoids played an important role in resisting severe influenza virus infection through intestinal microorganisms. Flavonoids were degraded by intestinal microorganisms of *Clostridium butyricum* to produce metabolite of deaminotyrosine, which stimulated type I interferon signal pathway after being absorbed by human body and induced the upregulation of interferon stimulated gene (ISG) [51]. Thus, it enhanced the natural antiviral immune response of macrophages and regulated the functions of antigen presenting cells and T cells [52]. Sea buckthorn (*Hippophae rhamnoides* L.) was one of the important medicinal plants, which contained rich flavonoids with antiviral activity. Compared with the anti-influenza drug of oseltamivir, the ethyl acetate extract and methanol extract of sea buckthorn (*Hippophae rhamnoides* L.) had stronger anti-influenza effect [53]. Further analysis showed that the flavonoid aglycones and flavonoid monosaccharides of sea buckthorn (*Hippophae rhamnoides* L.) extract were highly correlated with the antiviral activity. Among them, flavonoid monosaccharides exerted strong antiviral activity by inhibiting the initial stage of virus replication [54]. The Tibetan medicine Wuwei sea buckthorn powder was screened by network pharmacology and computer simulation molecular docking method, and the results showed that 4 flavonoids (kaempferol, quercetin, glycyrrhizin, and glycyrrhizin isoflavanone) were the main active components in the treatment of novel coronavirus pneumonia. It had the strongest binding force with the target of novel coronavirus. It regulated multiple signal pathways through the action mode of "multi-component and multi-target" to achieve potential therapeutic efficacy against novel coronavirus pneumonia [55].

6.2. Anti-Inflammatory. In recent years, immunotherapy with medicinal plants and their bioactive components as immunomodulators have gradually replaced traditional therapies such as drug therapy [56]. As immunomodulators, plant extracts have the advantages of easy access, simple preparation, less side effects, and strong efficacy. Previous studies proved that the inflammatory reaction of the body was closely related to intestinal microorganisms. Lipopolysaccharide (LPS) was a component of the cell wall of Gram-negative bacteria. Disordered intestinal flora aggravated LPS endotoxin to stimulate the body to secrete tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-4 (IL-4), interleukin-13 (IL-13), and protease activated receptor-2 (PAR-2), which destroyed the intestinal barrier, leading to tissue inflammation and immune response [57]. It was found that myricetin reduced inflammation by regulating butyric acid producing intestinal microorganisms (Allobaculum sp., Nocardiaceae, and Lachnospiraceae) and protecting intestinal barrier function. The flavonoids from sea buckthorn (*Hippophae rhamnoides* L.) inhibited the production of nitric oxide (NO) and the secretion of proinflammatory factors such as TNF-α, IL-6, and cyclooxygenase-2 (COX-2) [58]. At the same time, sea buckthorn (*Hippophae rhamnoides* L.) flavonoids promoted the expression of ZO-1 and occludin mRNA in intestinal tight junction proteins, repaired intestinal mucosa, and played an anti-inflammatory role in inhibiting the signal pathway of NOD-like receptor thermal protein domain associated protein 3 inflammatory bodies and related molecules [59].

6.3. Hepatoprotective. The sedentary lifestyle, excessive dietary calories, and excessive obesity will cause liver fat anabolism disorder and excessive deposition of free fatty acids, leading to liver injury. With the development of big data and evidence-based medicine, the unique pharmacological activity of natural active ingredients in protecting the liver had been further explored [60]. Flavonoids attracted the attention of scholars at home and abroad due to their extensive pharmacological effects and low toxicity. It was found that intake of foods rich in flavonoids was beneficial to liver protection. Based on the animal model of liver steatosis, it was found that the metabolism of 3,4-dihydroxybenzoic acid, 3,4,5-trihydroxybenzoic acid, 3,5-dimethoxy-4-hydroxybenzoic acid, and other metabolites produced by flavonoids through intestinal microbial decomposition

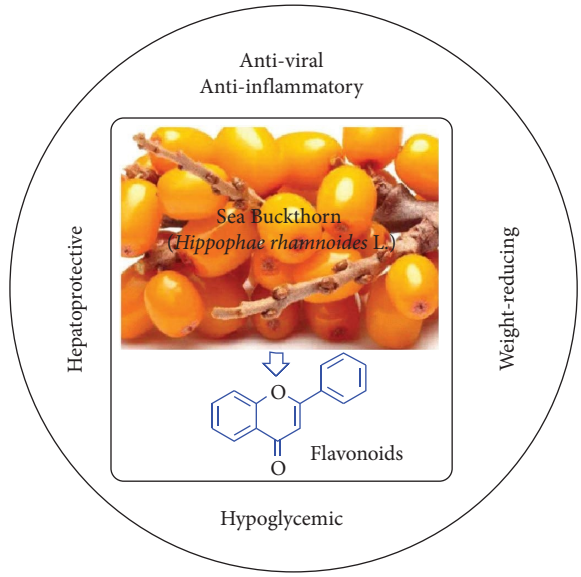


Figure 2: The bioactivities of flavonoids from sea buckthorn (*Hippophae rhamnoides* L.). Note: there were five kinds of bioactivities of flavonoids from sea buckthorn (*Hippophae rhamnoides* L.), including hepatoprotective, antiviral, anti-inflammatory, hypoglycemic, and weight-reducing activities.

improved the symptoms of fatty liver by changing the liver lipid metabolism [61]. The flavonoids of sea buckthorn (*Hippophae rhamnoides* L.) reduced the levels of alanine aminotransferase (ALT) and glutamic oxaloacetic transaminase (GOT) in serum and the contents of free fatty acid, cholesterol, and triglyceride in liver tissue of rats with nonalcoholic fatty liver model and activated the receptor by activating the adenosine 5′-monophosphate (AMP)-activated protein kinase-peroxisome proliferator-activated receptor-α (PPAR-α), which reduced the accumulation of lipid to alleviate the damage of nonalcoholic fatty liver in rats [62]. In addition, sea buckthorn (*Hippophae rhamnoides* L.) flavonoids reduced nuclear factor-k-gene binding (NFkB), mitogen-activated protein kinase (MAPK), and transforming growth factor-β (TGF-β) in liver, which activated the expression of TGF-activated kinase 1 (TAK-1) and mRNA and improved the liver damage in mice with alcoholic fatty liver disease. At the same time, the high-throughput sequencing results of 16S RNA gene showed that sea buckthorn (*Hippophae rhamnoides* L.) flavonoids effectively improved the richness and evenness of intestinal flora in mice with alcoholic liver injury and improved intestinal flora disorder [63].

6.4. Weight-Reducing. At present, overweight and obesity have become a global epidemic trend, which have gradually become a public health problem that cannot be ignored. Obesity is a phenomenon of excessive fat accumulation caused by energy intake exceeding energy consumption, which is closely related to obesity, dyslipidemia, insulin resistance, nonalcoholic fatty liver disease, and other chronic diseases [64]. Dietary supplementation of active substances rich in flavonoids reshaped the structure and composition of intestinal flora, protected intestinal health, and effectively interfered with obesity caused by high-fat diet [65]. Based on the obese animal model, it was found that metabolites produced by plant flavonoids through intestinal microbial decomposition, such as *p*-hydroxyphenylpropionic acid, 4-hydroxyacetic acid, and 4-hydroxymethoxybenzoic acid, inhibited liver adipogenesis and induced the upregulated expression of thermogenic factors in adipose tissue to promote fat decomposition and improve obesity symptoms caused by high-fat diet [61]. In addition, the regulation of flavonoids on body fat metabolism affected the expression of genes and transcription factors related to fat metabolism by mediating miRNAs, AMPK pathway activated by adenosine in liver tissue, mitotic clone expansion (MCE), and nervous system [66]. The study found that sea buckthorn (*Hippophae rhamnoides* L.) flavonoids significantly reduced the weight, liver fat accumulation, and serum triglyceride level of obese mice induced by high-fat diet and inhibited the chronic inflammatory reaction caused by obesity. The improvement effect of sea buckthorn (*Hippophae rhamnoides* L.) flavonoids on obesity and inhibition of peroxisome proliferator-activated receptor-γ (PPAR-γ) were proved by molecular level detection. The highest content of isorhamnetin and kaempferol effectively promoted fat decomposition. The flavonoid glycosides from sea buckthorn (*Hippophae rhamnoides* L.) reduced obesity and promoted energy consumption by inhibiting the synthesis and absorption of fat in adipose tissue of high-fat diet mice. In addition, these compounds improved the harmful effects of diet-induced obesity and metabolic complications (such as dyslipidemia, inflammation, and liver steatosis) and regulated the metabolic disorder caused by obesity [67].

6.5. Hypoglycemic. With the improvement of living standards, the aggravation of aging, and the increase of obese people, the number of diabetes patients is also increasing year by year. In the animal model of type 2 diabetes,

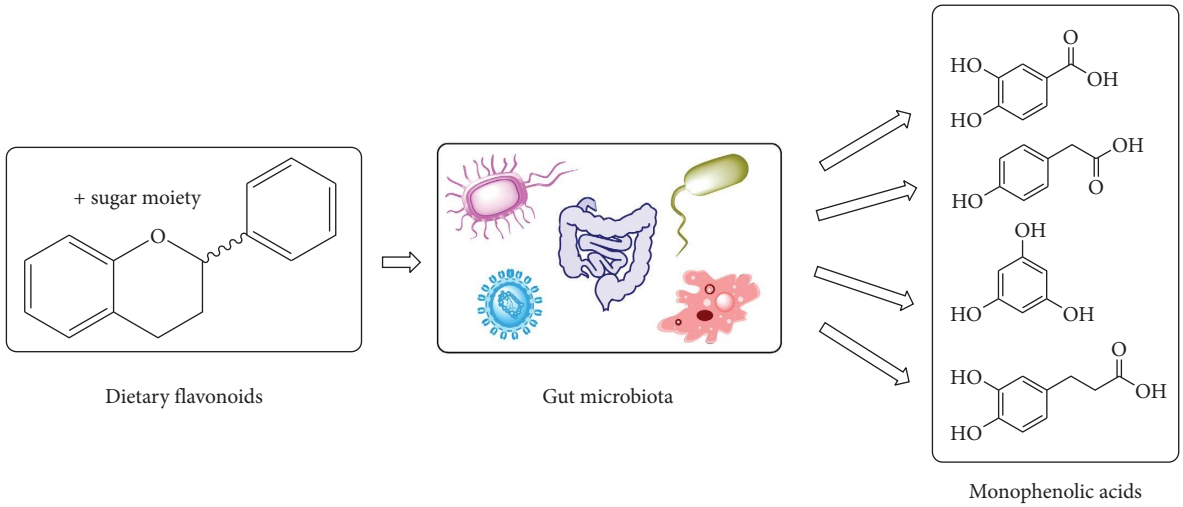


Figure 3: Gut microbial catabolism of dietary flavonoids into monophenolic acids. Note: the flavonoids of sea buckthorn (*Hippophae rhamnoides* L.) were catabolized into dietary flavonoids firstly and then further metabolized into monophenolic acids.

metabolites such as 3,4-dihydroxybenzoic acid, 3,4,5-trihydroxybenzoic acid, and 4-hydroxy-3-methoxybenzoic acid were produced by the decomposition of flavonoids by intestinal flora. These metabolites increased insulin sensitivity by regulating the phosphorylation of insulin receptor substrate 1 (IRS1) and protein kinase B (PKB) and improved glucose homeostasis and insulin resistance by reducing the activity of protein tyrosine phosphatase 1B (PTP-1B) [61]. The flavonoids from sea buckthorn (*Hippophae rhamnoides* L.) were the important hypoglycemic plant active substances. Relevant studies proved that the flavonoid glycosides of sea buckthorn (*Hippophae rhamnoides* L.) prevented insulin resistance, improved glucose tolerance, and reduced blood glucose level by reducing the activity of glucose-6-phosphatase, inhibiting proinflammatory factors (TNF-α, IL-6, and IL-12) and gluconeogenesis [59]. In addition, the total flavonoids from sea buckthorn (*Hippophae rhamnoides* L.) significantly reduced the fasting blood glucose value of hyperglycemic model mice and played a hypoglycemic role. It was found that sea buckthorn (*Hippophae rhamnoides* L.) flavonoids significantly increased the glucose consumption of HepG2 cells on the model of insulin resistance, which proved that sea buckthorn (*Hippophae rhamnoides* L.) flavonoids had potential preventive and therapeutic effects on diabetes. The above results indicated that sea buckthorn (*Hippophae rhamnoides* L.) flavonoids, as the hypoglycemic ingredients, were used in the research and development and application of hypoglycemic products, but their mechanisms still need to be further explored [68].

7. Metabolism of Flavonoids

The flavonoids from sea buckthorn (*Hippophae rhamnoides* L.) mostly exist in the form of glycosylation or aglycone heterocyclic molecules. After ingestion by human body, only 5%~10% of them are directly absorbed [69]. Because of their limited absorption, rapid systemic metabolism, and excretion, they have low bioavailability. However, most of the flavonoids that are not absorbed in the small intestine can be converted into small molecule monophenolic acids through intestinal microbial catabolism in the colon (Figure 3). Compared with the mother nucleus of flavonoids, the bioavailability of monophenolic acid produced by intestinal flora metabolism was higher, which was easier to be absorbed by human body, and the content in human plasma reached micromolar concentration. The main active flavonoids of sea buckthorn included rutin, quercetin, kaempferol, isorhamnetin, myricetin, naringin, dihydromyricetin, proanthocyanidin B1, and other anthocyanins [70]. It was found that quercetin was converted into small molecules such as 3,4-dihydroxyphenylacetic acid and 4-hydroxybenzoic acid under the action of intestinal flora such as *Streptococcus* S-2, *Lactobacillus* L-2, *Bifidobacterium* B-9, and *Bacteroides* JY-6, which were absorbed and utilized by human body. Among them, the small molecule of 3,4-dihydroxyphenylacetic acid improved insulin secretion, glucose metabolism, and liver injury in mice induced by acetaminophen [71–73]. The process of absorption and metabolism of flavonoids of sea buckthorn (*Hippophae rhamnoides* L.) was a complex process completed by the interaction and cooperation of a variety of intestinal microorganisms. The intestinal microorganisms promoted the transformation of flavonoids into bioactive metabolic molecules and improved the metabolism, absorption, bioavailability, and physiological activity of flavonoids in the body. Therefore, the production of various physiological functions of sea buckthorn flavonoids in human body depended on the catabolism of intestinal microorganisms, which mainly affected human health by changing the structure of intestinal flora and the enzyme system to catabolize different bioactive small molecules. However, the functional mechanism of flavonoids from sea buckthorn (*Hippophae rhamnoides* L.) as prebiotics will need further research in the future.

8. Conclusion and Perspective

8.1. Conclusion. To sum up, sea buckthorn (*Hippophae rhamnoides* L.) is an important medicinal and edible plant, which attracts the attention of researchers in the world. Especially, the flavonoids from sea buckthorn (*Hippophae rhamnoides* L.) have been the focus of research in recent years [62, 74, 75]. This review comprehensively summarized extraction methods (solvent extraction, ultrasound-assisted extraction, microwave-assisted extraction, enzyme-assisted extraction, and collaborative extraction), structure types (flavone aglycones and flavone glycosides), detection methods (UV, HPLC, and NMR), bioactivities (antiviral, anti-inflammatory, hepatoprotective, weight-reducing, and hypoglycemic activities), and metabolism of flavonoids from sea buckthorn (*Hippophae rhamnoides* L.). This highly compact summarization in the present review could launch a bridge for the ongoing scientific studies and supply researchers with new direction.

8.2. Perspective. Sea buckthorn (*Hippophae rhamnoides* L.), as a medicinal and edible plant, has the value of deep development and comprehensive utilization of high quality. At present, the development of sea buckthorn (*Hippophae rhamnoides* L.) products covers many fields such as medicine, food, health products, and cosmetics. However, the in-depth study and all-round application of sea buckthorn (*Hippophae rhamnoides* L.) still have some shortcomings, including the potential mechanism of flavonoids with biological activities, quality control, potential toxicity, structure-activity relationships of flavonoids, and so on. Sea buckthorn flavonoids contained many small molecule functional components, including quercetin, isorhamnetin, and other flavonoids. They played an important role in the development of medicine and functional food, but most studies focused on the *in vitro* function evaluation. Therefore, sea buckthorn flavonoids are functional substances with good development potential. Future research studies need focus on clarifying the molecular mechanism between low bioavailability and different pharmacological activities of sea buckthorn flavonoids in the future.

The efficacy mechanism and clinical application of flavonoids from sea buckthorn were clarified by metagenomics, proteomics, transcriptome, metabolomics, and other technologies. It will help further explore the prebiotic function of flavonoids from sea buckthorn, which benefit to develop methods and technologies to improve the bioavailability of flavonoids from sea buckthorn. Meanwhile, it will further promote the precise nutrition research of flavonoids in sea buckthorn and the development of personalized nutritional diet, promote the high-value utilization and industrial development of sea buckthorn (*Hippophae rhamnoides* L.) and other drug food homologous resources, and help the precise nutrition regulation technology and the future development of functional food creation.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Nengxin He, Qinyuan Wang, Jie Chen, Guang Wu, and Meining Zhu were responsible for investigation, data curation, and formal analysis. Huilian Huang, Feng Shao, and Zhihong Yan were responsible for methodology and conceptualization. Zhipei Sang, Lan Cao, Rongrui Wei, and Qinge Ma were responsible for original draft preparation, supervision, funding acquisition, and review and editing. All authors discussed and approved the final manuscript.

Acknowledgments

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