Isorhamnetin Glycosides as Phytonutrients

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Isorhamnetin glycosides (IGs) are a class of essential flavonoids derived from dietary and medicinal plants such as *Opuntia ficus-indica*, *Hippophae rhamnoides*, and *Ginkgo biloba*.

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1. Introduction

Phytonutrients are chemical compounds that are only present in natural plants and are beneficial to the human body [1]. They are widely used in food and nutraceuticals due to their health-promoting benefits [2]. Flavonoids are a class of polyphenolic compound distributed in many fruits, vegetables, and plants [3]. The six major subclasses of flavonoids, which include flavones (e.g., luteolin), flavonols (quercetin), flavanones (hesperidin), catechins or flavanols (epicatechin), anthocyanidins (cyanidin), and isoflavones (daidzein), have been reported to represent various families of phytonutrients [4]. Accumulating evidence based on observational and clinical studies shows that a plant-based dietary pattern rich in fruits, vegetables, and whole grains has a clear effect on the prevention of various chronic diseases [5], and people also tend to consume dietary flavonoids from fruits and vegetables. Flavonoids are widely found in food, and most of them exist in their glycosidic forms [6][7].

Isorhamnetin glycosides (IGs), as natural flavonol compounds, are primarily extracted from various plant-based foods or medicinal plants such as *Opuntia ficus-indica*, *Hippophae rhamnoides*, and *Ginkgo biloba* [8][9][10]. IGs are biologically important flavonols with proven beneficial properties that give them medicinal value [11][12]. They possess diverse biological and pharmacological properties, such as antioxidant, anti-inflammatory, anti-cancer, antidiabetic, anti-obesity, and hepatoprotective properties [13][14][15][16][17]. Due to their beneficial biological activities, IGs have been considered a significant potential class of phytonutrients, and an increasing number of products containing IGs are circulating on the market in many countries, including the United States, Canada, Mexico, China, India, and some European countries [18][19].

2. Structure of IGs

IGs are a type of glycosylated flavonol composed of an isorhamnetin skeleton and sugar groups. Their aglycone isorhamnetin, i.e., 3,4′,5,7-tetrahydroxy-3′-methoxyflavone, is an *O*-methylated flavonol (**Figure 1**). Generally, d-glucose, d-galactose, l-rhamnose, d-xylose, l-arabinose, sophorose, and rutinose are the most common sugar groups of IGs. They are linked to the aglycone by an *O*-glycosidic bond. According to the number of sugar groups, IGs are classified as mono-, di-, tri-, or tetra-glycosides. Position substitutions mostly happen at C-3 and C-7, for

example, isorhamnentin-3-*O*-β-d-glucoside (**4**) and isorhamnetin-3-*O*-β-d-glucoside-7-*O*-α-l-rhamnoside (**20**) from *Hippophae rhamnoids* [20]; isorhamnetin-3-*O*-α-l-rhamnoside (**3**) from Laportea bulbifera Wedd. [21]; and isorhamnetin-7-*O*-β-d-glucoside (**1**) and isorhamnetin-7-*O*-α-l-rhamnoside (**2**) from Nitraria tangutorum Bolor [22]. Of course, sometimes, substitution occurs at C-4′, for instance, isorhamnetin-4′-*O*-β-d glucoside (**9**) from Allium cepa L. [23]; isorhamnetin-3,4′-*O*-β-d-diglucoside (**17**) from Allium ascalonicum [24]; isorhamnetin-3-*O*-β-d -glucoside-4′-*O*-β-d-xyloside (**21**) [25]; and isorhammetin-3-*O*-α-l-rhamnoside-(1→6)-β-d-glucoside-4′-*O*-β-d-glucoside (**35**) [26]. In addition, some sugar group derivatives, such as isorhamnetin-3-*O*-[2‴-*O*-acetyl−β-d-xyloside-(1→6)-β-d-glucoside] (**10**) [27] and isorhamnetin-3-*O*-β-d (6-acetyl-glucoside) (**7**) [28], have also been obtained.

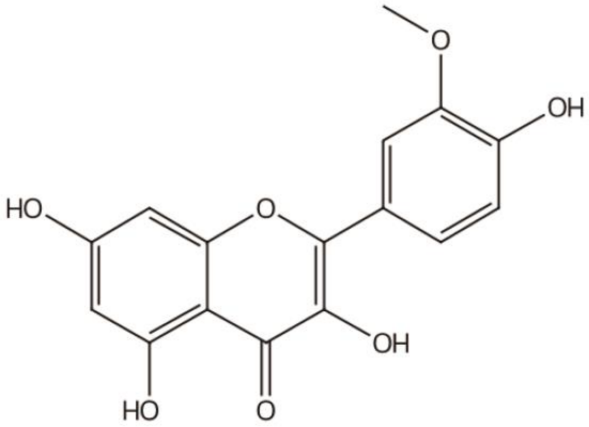
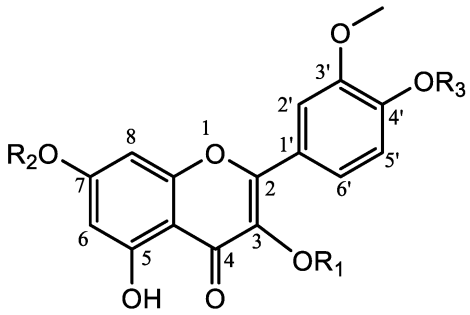


Figure 1. Basic parent nucleus of isorhamnetin glycosides (IGs).

Here, the researchers systematically summarize the 49 compounds of IGs reported thus far (**Table 1** and **Figure 2**).



	R_1	R_2	R_3
1	H	glc	H
2	H	rha	H
3	rha	H	H
4	glc	H	H
5	glccur	H	H
6	2-acetyl-glccur	H	H
7	6-acetyl-glc	H	H
8	gal	H	H
9	H	H	glc
10	2'''-O-acetyl-xyl-(1→6)-glc	H	H
11	[2''',3'''-O-isopropylidene--rha]-glc	H	H
12	H	rha-(1→2)-glc	H
13	glc-(1→6)-glc]	H	H
14	4'''-p-coumaroyl-rha(1→6)gal	H	H
15	rha-(1→2)-glc	H	H
16	xyl-(1→2)-gal	H	H
17	glc	H	glc
18	glc	glc	H
19	rha	rha	H
20	glc	rha	H
21	glc	H	xyl
22	rha-(1→6)-gal	H	H
23	rha-(1→2)-rha	H	H
24	rha-(1→6)-glc	H	H
25	apioide-(1→2)-gal	H	H
26			

28	glc-(1→2)- rha	H	H
29	2'''-*O*-acetyl-ara-(1→6)-gal	H	H
30	ara-(1→6)-gal	H	H
31	4''-acetyl-rha	rha	H
32	glc	ara	H
33	rha-(1→2)-gal	H	H
34	glc	3'''-isovaleryl-rha	H
35	rha-(1→6)-glc	H	glc
36	(2^{G}-apioside)-2'''-O-acetyl-xyl-(1→6)-glc	H	H
37	(2'', 6''-dirha)-gal	H	H
38	(4^{Rham}-gal)- rha-(1→6)-gal	H	H
39	rha-(1→2)-gal	glc	H
40	rha-(1→6)-glc	rha	H
41	glc-(1→2)-glc	glc	H
42	xyl-(1→3^{Rham})-rha-(1→2)-gal	H	H
43	glc-(1→2)-glc	rha	H
44	[(6-*O*-E-sinapoyl)-glc-(1→2)]-glc	rha	H
45	(2^{G}-rha)-rha-(1→6)-glc	H	H
46	(2^{G}-glc)-rha-(1→6)-glc	H	H
47	rha-(1→6)-glc	glc	H
48	glc	glc-(1→6)-glc	H
49	[2^{G}-rha-(1→6)-glc]-rha-(1→6)-glc	H	H

Figure 2. Chemical structures of IGs (compounds **1**–**49**). Monoglycosides (**1–9**), diglycosides (**10–34**), triglycosides (**35–48**), and tetraglycosides (**49**). Abbreviations: Glc: D-glucose, Rha: L-rhamnose, Glccur: D-glucuronic, Gal: D-galactose, Xyl: D-xylose, Ara: L-arabinose. Abbreviations: Glc: d-glucose, Rha: l-rhamnose, Glccur: d-glucuronic, Gal: d-galactose, Xyl: d-xylose, Ara: l-arabinose.

Table 1. Isorhamnetin glycoside (IG) compounds (**1–49**). According to the number of sugar groups, IGs are divided into monoglycosides (**1–9**), diglycosides (**10–34**), triglycosides (**35–48**), and tetraglycosides (**49**).

No.	Name	Trivial Name	Source	Ref.
Monoglycosides				

No.	Name	Trivial Name	Source	Ref.
1	Isorhamnetin-7-*O*-β-d-glucoside	Brassicin	*Centaurea cyanus* *Centaurea kotschyi* var. *kotschyi* *Cnicus wallichi* *Russowia Sogdiana* *Tagetes lucida* (Asteraceae) *Sedum sarmentosum* Bunge *Nitraria tangutorum* Bolor	[29] [30] [31] [32] [33] [34] [22]
2	Isorhamnetin-7-*O*-α-l-rhamnoside		*Carduncellus eriocephalus* *Nitraria tangutorum* Bolor *Atriplex centralasiatica* *Laportea bulbifera* Wedd. *V. galamensis* ssp. *galamensis var. petitiana* (A. Rich) M. Gilbert *Raphanus raphanistrum* L. *Caragana intermedia*	[35] [22] [36] [21] [37] [38] [39]

No.	Name	Trivial Name	Source	Ref.
3	Isorhamnetin-3-*O*-α-l-rhamnoside		*Laportea bulbifera* Wedd.	[21]
4	Isorhamnentin-3-*O*-β-d-glucoside		*Astragalus centralpinus*	[40]
			Solidago canadensis L.	[28]
			Hippophae rhamnoids	[20]
			Sambucus nigra L.	[41]
			Calendula officinalis	[42]
5	Isorhamnetin-3-*O*-β-d-glucuronide		*Arnica montana*	[43]
			Persicaria thunbergii	[44]
			Senecio giganteus	[45]
			Polygonum aviculare L.	[46]
			Senecio argunensis Turcz.	[47]
6	Isorhamnetin-3-*O*-β-d-(2-acetyl-glucuronide)		*Polygonum aviculare* L.	[46]
7	Isorhamnetin-3-*O*-β-d (6-acetyl-glucoside)		*Solidago canadensis* L.	[28]
8	Isorhamnetin-3-*O*-β-d-galactoside		*Senecio argunensis* Turcz.	[47]

No.	Name	Trivial Name	Source	Ref.
9	Isorhamnetin-4′-*O*-β-d glucoside		*Allium cepa* L.	[23]
Diglycosides				
10	Isorhamnetin-3-*O*-[2‴-*O*-acetyl−β-d-xyloside-(1→6)-β-d-glucoside]		*Gymnocarpos decander*	[27]
11	Isorhamnetin-3-*O*-[2‴,3‴-*O*-isopropylidene-α-l-rhamnoside]—(1→6)-β-d-glucoside		*Tetraena aegyptia*	[48]
12	Isorhamnetin-7-*O*-α-l-rhamnoside-(1→2)-β-d-glucoside	Isorhamnetin-7-*O*-β-neohesperidoside	*Cleome droserifolia*	[12]
13	Isorhamnetin-7-*O*-β-d-glucoside-(1→6)-β-d-glucoside	Astragaloside or Isorhamnetin-7-*O*-gentiobioside	*Astragalus altaicus*	[49]
14	Isorhamnetin-3-*O*-β-(4‴-p-coumaroyl-α-rhamnosy]—(1→6)-galactoside)		*Aerva javanica*	[50]
15	Isorhamnetin-3-*O*-α-l-rhamnoside-(1→2)-β-d-glucoside	Isorhamnetin-3-*O*-β-neohesperidoside	*Hippophae rhamnoids* *Typha augustifolia* L. *Calendula officinalis*	[20] [51] [42]

No.	Name	Trivial Name	Source	Ref.
16	Isorhamnetin-3-*O*-β-d-xylosidel-(1→2)-β-d-galactoside		*Prunus padus* L.	[52]
17	Isorhamnetin-3,4′-*O*-β-d-diglucoside		*Allium ascalonicum* *Lepidium apetalum* willd	[24] [53]
18	Isorhamnetin-3,7-*O*-β-d-diglucoside		*Sedum sarmentosum* Bunge *Carduncellus eriocephalus*	[34] [35]
19	Isorhamnetin-3,7-*O*-α-l-dirhamnoside		*Laportea bulbifera* Wedd.	[21]
20	Isorhamnetin-3-*O*-β-d-glucoside-7-*O*-α-l-rhamnoside	Brassidine	*Sinapis arvensis* *Atriplex centralasiatica* *Hippophae rhamnoids*	[54] [36] [20]
21	Isorhamnetin-3-*O*-β-d-glucoside-4′-*O*-β-d-xyloside		*Diplotaxis harra* (Forssk.) Boiss	[26]
22	Isorhamnetin-3-*O*-α-l-rhamnoside-(1→6)-β-d-galactoside	Isorhamnetin-3-*O*-robinobioside	*Nitraria retusa*	[55]
23	Isorhamnetin-3-*O*-α-rhamnoside-(1→2)-rhamnoside		*Laportea bulbifera* Wedd.	[21]

No.	Name	Trivial Name	Source	Ref.
24	Isorhamnetin-3-*O*-α-l-rhamnoside-(1→6)-β-d-glucoside	Narcissin Isorhamnetin-3-*O*-rutinoside	*V. galamensis* ssp. *galamensis var.* petitiana (A. Rich) M. Gilbert *opuntia ficus-indica* *Hippophae rhamnoids* *Ginkgo biloba* *Sambucus nigra* L. *Calendula officinalis*	[37] [18] [20] [9] [56] [41] [42]
25	Isorhamnetin-3-*O*-β-d-apioide (1→2)-β-d-galactoside		*V. galamensis* ssp. *galamensis var. petitiana* (A. Rich) M. Gilbert	[37]
26	Isorhamnetin-3-*O*-α-l-arabinoside-7-*O*-β-d-glucoside		*Callianthemum taipaicum* *Narcissus pseudonarcissus*	[57] [58]
27	Isorhamnetin-3-*O*-β-d- (6‴-p-coumaroyl-α-glucoside-(1→2)-rhamnoside)		*Ginkgo biloba*	[56]
28	Isorhamnetin-3-*O*-β-d-glucoside-(1→2)-α-l-rhamnoside		*Ginkgo biloba*	[56]

No.	Name	Trivial Name	Source	Ref.
29	Isorhamnetin-3-*O*-[2‴-*O*-acetyl−α-l-arabinoside-(1→6)-β-d-galactoside]		*Trillium tschonoskii* Maxim. *Trillium apetalon* Makino. and *T. kamtschaticum* Pallas.	[59] [60]
30	Isorhamnetin-3-*O*−α-l-arabinoside-(1→6)-β-d-galactoside		*Trillium apetalon* Makino. and *T. kamtschaticum* Pallas.	[60]
31	Isorhamnetin-3-*O*-α-(4″-acetyl-rhamnoside)-7-*O*-α-rhamnoside		*Cleome droserifolia*	[12]
32	Isorhamnetin-3-*O*-β-d-glucoside-7-*O*-α-l-arabinoside		*Eschscholtzia* mexicana Greene	[61]
33	Isorhamnetin-3-*O*-α-l-rhamnoside(1→2)]-β-d-galactoside		*Glycine max* (L.) Merr.	[62]
34	Isorhamnetin-3-*O*-β-glucoside-7-*O*-α-(3‴-isovaleryl)-rhamnoside		*Lepidium apetalum*	[53]
Triglycosides				
35	Isorhamnetin-3-*O*-α-l-rhamnoside-(1→6)-β-d-glucoside-4′-*O*-β-d-glucoside	Isorhamnetin-3-rutinoside-4′-glucoside	*Mercurialis annua*	[26]

No.	Name	Trivial Name	Source	Ref.
36	Isorhamnetin-3-*O*-(2^{G}-β-d-apiofuranosyl) [2‴-*O*-acetyl−β-d-xyloside-(1→6)-β-d-glucoside]		*Gymnocarpos decander*	[27]
37	Isorhamnetin-3-*O*-(2″,6″-*O*-α-l-dirhamnoside)-β-d-galactoside		*Alangium premnifolium* *Lysimachia fortunei*	[63] [64]
38	Isorhamnetin-3-*O*-(4^{Rham}-β-d-galactosyl)-α-l-rhamnoside-(1→6)-β-d-galactoside]	Isorhamnetin-3-*O*-4^{Rham}-galactosyl-robinobioside	*Nitraria retusa*	[55] [65]
39	Isorhamnetin-3-*O*-α-l-rhamnoside-(1→2)-β-d-galactoside-7-*O*-β-d-glucoside		*Blackstonia perfoliata*	[66]
40	Isorhamnetin-3-*O*-α-l-rhamnoside-(1→6)-β-d-glucoside-7-*O*-α-l-rhamnoside	Isorhamnetin-3-rutinoside-7-rhamnoside	*Cassia italica* *Hippophae rhamnoides*	[67] [68]
41	Isorhamnetin-3-*O*-β-glucoside-(1→2)-β-d-glucoside-7-β-d-glucoside	Brassicoside or Isorhamnetin-3-*O*-sophoroside-7-*O*-β-d-glucoside	*Brassica napus*	[54]
42	Isorhamnetin-3-*O*-β-d-xyloside-(1→3^{Rham})-α-l-rhamnoside-(1→6)-β-d-galactoside	Isorhamnetin 3-xylosyl-robinobioside	*Nitraria retusa*	[55]
43	Isorhamnetin-3-*O*-β-glucoside-(1→2)-β-d-	Isorhamnetin-3-*O*-sophoroside-7-*O*-	*Hippophae rhamnoids*	[20]

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myrtillus,
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folium, *Sambucus nigra*, and *Calendula officinalis* (**Figure 3**).

No.	Name	Trivial Name	Source	Ref.
	glucoside-7-*O*-α-l-rhamnoside	rhamnoside		
44	Isorhamnetin-3-*O*-[(6-*O*-E-sinapoyl)-β-d-glucoside-(1 → 2)]-β-d-glucoside-7-*O*-α-l-rhamnoside		*Hippophae rhamnoids*	[20]
45	Isorhamnetin-3-*O*-(2^{G}-α-l-rhamnoside)-α-l-rhamnoside-(1→6)-β-d-glucoside	Typhaneoside	*Typha augustifolia* L. *Calendula officinalis*	[51] [42]
46	Isorhamnetin-3-*O*-(2^{G}-β-d-glucoside)-α-l-rhamnoside-(1→6)-β-d-glucoside		*Boldo Folium*	[69]
47	Isorhammetin-3-*O*-α-l-rhamnoside-(1→6)-β-d-glucoside-7-*O*-β-d-glucoside	Isorhammetin-3-rutinoside-7-glucoside	*Hippophae rhamnoids* *Mercurialis annua*	[20] [26]
48	Isorhamnetin-3-*O*-β-d-glucoside-7-*O*-β-d-glucoside-(1→6)-β-d-glucoside	Isorhamnetin-3-*O*-glucoside-7-*O*-gentiobioside	*Lepidium apetalum* willd	[53]
Tetraglycosides				
49	Isorhamnetin-3-*O*-[2^{G}-α-l-rhamnoside-(1→6)-β-d-glucoside]-α-l-rhamnoside-(1→6)-β-d-glucoside		*Boldo Folium*	[69]

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NMR have been used to determine the structure of IGs.

4.2. Chromatographic Techniques

IGs can be distinguished from each other on the basis of chromatographic techniques. Therefore, the analysis, characterization, and quantification of IGs are usually performed using the following chromatographic techniques: TLC, HPLC, UPLC, and HSCCC.

5. The Health-Promoting Effects of IGs

IGs possess a variety of biological properties, including antioxidant, anti-inflammatory, and anti-cancer properties. Research has recently been undertaken to investigate their pharmacological benefits for the treatment of various diseases, such as diabetes, obesity, hepatic diseases, and thrombosis.

5.1. Antioxidant Activity

Oxidative damage induced by free radicals results in detrimental outcomes, such as a loss of cellular function and the dysfunction of organic systems [70]. It is worth mentioning that numerous in vitro and in vivo studies have demonstrated the strong antioxidant and radical-scavenging properties of IGs.

β-carotene-linoleic acid, 2,2-diphenyl-1-picrylhydrazil (DPPH) scavenging, 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonate) (ABTS), oxygen radical absorbance capacity (ORAC), peroxyl radical-scavenging capacity (PSC), superoxide scavenging, peroxynitrite (ONOO(-)) assays, and CUPric reducing antioxidant capacity (CUPRAC) are commonly used indirect assays for identifying antioxidant activity. IGs isolated from the stamens of Nelumbo nucifera showed significant antioxidant activity, as determined via DPPH and ONOO(-) assays [11]. Brassicin (**1**) exhibited stronger free radical-scavenging ability than vitamin C [13] and exhibited DPPH radical- and ONOO(-)-scavenging activity [71]. Isorhamnetin 3-*O*-robinobioside (**22**), isorhamnetin 3-*O*-(2″,6″-*O*-α-dirhamnosyl)-β-galactoside (**37**) [72], typhaneoside (**45**), and isorhamnetin 3-*O*-neohesperidoside (**15**) [73] have been demonstrated to exhibit antioxidant activity using a DPPH radical-scavenging activity assay. Astragaloside (**13**) and narcissin (**24**) possessed antioxidant capacity, which was evaluated using ABST [74]. Narcissin (**24**) and isorhamnetin 3-*O*-rutinoside-7-*O*-glucoside (**47**) exhibited obvious antioxidant activity, which was detected using DPPH, β-carotene-linoleic acid, and ABST [65][75]. Isorhamnetin 3-*O*-neohesperidoside (**15**) was a potent inhibitor of xanthine oxidase and superoxide anion scavengers [76]. Furthermore, researchers have revealed the antioxidant properties of isorhamnetin 3-*O*-glucoside (**4**) and isorhamnetin 3-*O*-galactoside (**8**) in all the antioxidant activity tests employed [77][78][79][80].

Evaluation of the antioxidant properties of IGs were also carried out using various cell type experiments and animal models. The oral administration of isorhamnetin-3,7-diglucoside (**18**) to streptozotocin-induced diabetic rats significantly reduced their levels of 5-(hydroxymethyl) furfural (5-HMF), which is an indicator of the glycosylation of hemoglobin, and of stress [81]. Similarly, isorhamnetin 3-*O*-robinobioside (**22**) exhibited significant antioxidant effects on the human chronic myelogenous leukemia cell line K562 [82]. IGs had the ability to inhibit the formation of H_2O_2-induced radicals in the surrounding environment of intestinal epithelial cells [83]. Moreover, the transcriptional genes of the antioxidant system and the DNA repair pathway were upregulated after incubation with isorhamnetin 3-*O*-neohesperidoside (**15**) in pKS plasmid DNA [84]. Narcissin (24) and isorhamnetin 3-*O*-glucoside (**4**) demonstrated strong inhibition of reactive oxygen species (ROS) production in the oxidative burst activity of whole blood, neutrophils, and mononuclear cells [85]. Plant extracts rich in IGs also exhibited antioxidant activity. IG-rich concentrate from *Opuntia ficus-indica* juice had the ability to inhibit the formation of H_2O_2-induced radicals in the surrounding environment of intestinal epithelial cells [86]. The total antioxidant activity of *Hippophae rhamnoides*

berry extracts, evaluated via ORAC and PSC, was significantly associated with total phenolics, including isorhamnetin-3-rutinoside (**24**) and isorhamnetin-3-glucoside (**4**) [87].

5.2. Anti-Inflammatory Activity

IGs have anti-inflammatory properties due to different mechanisms. As an important inflammatory mediator, high-mobility-group protein 1 (HMGB1) contributes to organ damage and inflammation [88]. Isorhamnetin 3-*O*-galactoside (**8**) (5 μM) has been demonstrated to significantly inhibit the release of HMGB1 and reduce HMGB1-dependent inflammatory responses in human endothelial cells. It was found that **8** (4.8 mg/mouse) could also inhibit HMGB1 receptor expression, the HMGB1-mediated activation of NF-kB, and the production of tumor necrosis factor (TNF-α) in mice [89].

Mitogen-activated protein kinase (MAPK) signaling pathways, including p38, c-Jun *N*-terminal kinase (JNK), and extracellular regulated kinases (ERK), play crucial roles in inflammatory responses [90]. Isorhamnetin 3-*O*-galactoside (**8**) (50 μM) reduced cecal ligation and endothelin C receptor perforation-mediated shedding and down-regulated the phosphorylation of p38 MAPK, ERK 1/2, and JNK [14]. Similarly, isorhamnetin 3-*O*-glucuronide (**5**) exhibited anti-inflammatory activity by increasing heme oxygenase-1 (HO-1) expression and suppressing the JNK and p38 signaling pathways in LPS-induced RAW264.7 macrophage cells [91]. Moreover, isorhamnetin 3-*O*-glucuronide (**5**) inhibited the production of ROS (10 μM), as well as the release of elastase, in a human neutrophil model (1 μM) and suppressed the upregulation of inducible nitric oxide synthase (iNOS) expression (5 μM), and could be considered to display anti-inflammatory activity [46][92].

Many studies have shown the anti-inflammatory properties of IGs by inhibiting inflammatory cytokines. The inflammatory activity of narcissin (**24**) (100 μM) and isorhamnetin 3-*O*-glucoside (**4**) (100 μM) was mediated via the inhibition of nuclear factor kappa-B (NFκB) and inflammatory mediators such as TNF-α, interleukin-1β (IL-1β), and interleukin-6 (IL-6) in phytohaemagglutinin-stimulated human peripheral blood mononuclear cells (PBMC) [83]. Likewise, narcissin (**24**) (40 μM) achieved the inhibition of inflammatory cytokines (TNF-α, IL-1β, and IL-6) in advanced glycation end product (AGE)-induced RAW264.7 cells [93]. Isorhamnetin-3-*O*-[2,3-*O*-isopropylidene-α-l-rhamnopyranosyl]-(1→6)-*O*-β-d-glucopyranoside (**11**) (25 μM) showed a significant inhibitory effect on NO release and the secretion of the cytokines IL-6 and TNF-α [48]. Isorhamnetin-3,4′-diglucoside (**17**) (100 μg/mL) and isorhamnetin 3-*O*-glucoside (**4**) (100 μg/mL) have shown the inhibitory effect of IL-6 production on TNF-α-stimulated human osteosarcoma MG-63 cells [94]. Isorhamnetin 3-O-glucoside (**4**) (100 μg/mL) showed distinct anti-inflammatory activity with no toxicity on RAW 264.7 macrophage cells as compared to dexamethasone [95]. Seddik Ameur et al. studied the anti-inflammatory activity of IGs extracted from *Opuntia ficus-indica* flowers, and their results showed that isorhamnetin-3-*O*-robinobioside (**22**) is the product responsible for the anti-inflammatory activity [96]. Both Opuntia ficus-indica extract (OFI-E) and isorhamnetin-3-*O*-rhamnosylglucoside (**24**) (125 ng/mL) significantly inhibited cyclooxygenase-2 (COX-2), TNF-α, and IL-6 production, of which 24 compounds have been suggested to be suitable natural compounds for the development of a new anti-inflammatory ingredient [97]. The total flavonoid-rich IGs from sea buckthorn exhibited a protective effect against LPS/CS-induced airway

inflammation by inhibiting the ERK, PI3K/Akt, and PKCα pathways and diminishing the expression of IL-1β, IL-6, and COX2 in mice [98].

5.3. Anti-Cancer Activity

Flavonoids have great potential for anticancer prevention [99]. IGs have also been proven to possess anticancer effects. Brassicin (**1**) (22.8 μg/mL) showed in vitro cytotoxicity against human colon cancer cells in the HCT116 cell line [100]. Isorhamnetin 3-*O*-neohesperidoside (**15**) (2.47 μg/mL) showed potent cytotoxicity against breast ductal carcinoma and colorectal adenocarcinoma (Caco-2) cells [101]. Narcissin (**24**) showed cytotoxic effects in Hela cells and the hormone dependent prostate carcinoma LNCaP cell line (IC_{50} = 20.5 μg/mL) [102][103].

Mechanically, IGs have been involved in the induction of apoptosis and the inhibition of cancer cell proliferation (**Figure 4**A). Apoptosis, the most vital cell death mechanism, ultimately contributes to tumor progression [104]. Mitochondria play an essential role in cell death signaling and ROS generation [105]. The production of ROS above a threshold level can trigger apoptosis in cancer cells, thereby limiting further cancer progression [106]. After the excessive production of ROS, the expression of genes related to the mitochondrial apoptosis pathway (Bax, Caspase9, and Caspase3) was aggravated, and the expression of the anti-apoptotic gene Bcl-2 was reduced [107]. Emerging evidence suggests that IGs promote ROS generation and the activation of mitochondria-dependent apoptosis in cancer cells (**Figure 4**B).

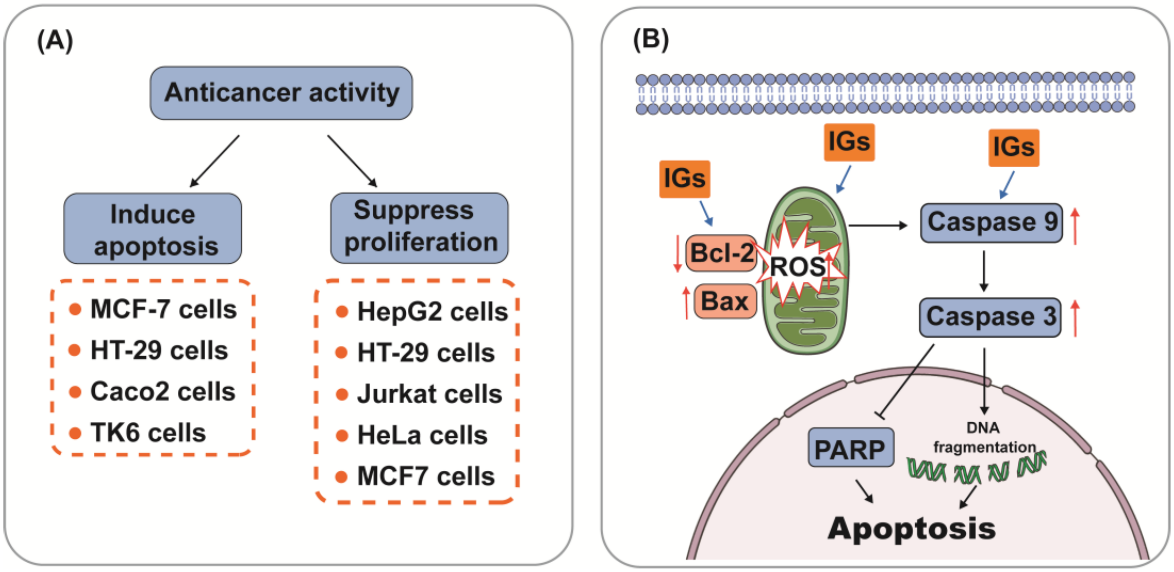

Figure 4. Anticancer activity (**A**) and mechanism of regulating the apoptotic pathway (**B**) of IGs.

5.4. Hepatoprotective Ability

The liver is the most essential and functional organ in the body, and it is where primary detox and metabolic events occur [108]. Liver injury can be caused by various factors, including alcohol, microbial infection, drugs, biological

toxins, and chemical agents [109]. Flavonoids in many different foods and medicinal plants have therapeutic potential in liver disease [110].

Studies have confirmed that IGs play an important role in liver injury by modulating multiple pathways (**Figure 5**). The hepatoprotective effects of IGs are closely linked with their antioxidant and anti-inflammatory effects. Isorhamnetin 3-*O*-galactoside (**8**) (100 mg/kg) reduced serum TNF-α levels, aminotransferase activities, and the hepatic level of malondialdehyde (MDA); attenuated increases in iNOS and COX-2 protein and mRNA expression levels; attenuated increases in nuclear factor kappa-B (NF-κB) and c-Jun nuclear translocation; and augmented the levels of HO-1 and mRNA expression and the nuclear level of nuclear factor E2-related factor 2 (Nrf2) in a carbon tetrachloride (CCl_4)-induced hepatic damage model (**Figure 5**A). This suggests that IGs exhibit hepatoprotective effects by enhancing the antioxidative defense system and reducing the inflammatory signaling pathways [16]. A similar result was obtained for the hepatoprotective effects of isorhamnetin 3-*O*-glucoside (**4**) (20 μg/mL/mouse). It suppressed the increase in plasma alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities in CCl_4-induced liver injury mice [111]. *Opuntia ficus-indica* fruit juice (3 mL/rat) administration exerted protective and curative effects against the CCl_4-induced degenerative process in rat liver [112]. The oral administration of a phenolic-rich fraction of sea buckthorn leaves (25–75 mg/kg) significantly protected against CCl_4-induced elevation in AST, ALT, c-glutamyl transpeptidase, and bilirubin in the serum, and also protected against histopathological changes produced by CCl_4, such as hepatocytic necrosis, fatty changes, and vacuolation [113]. In another study, typhaneoside (**45**) exhibited hepatoprotective effects on D-GalN-induced cytotoxicity in primary cultured mouse hepatocytes [114]. The phytochemical constituents of cactus branch extract (92 mg/kg), which were found to possess excellent antioxidant properties, had protective effects against lithium-induced hepatotoxicity and oxidative stress in rats [115].

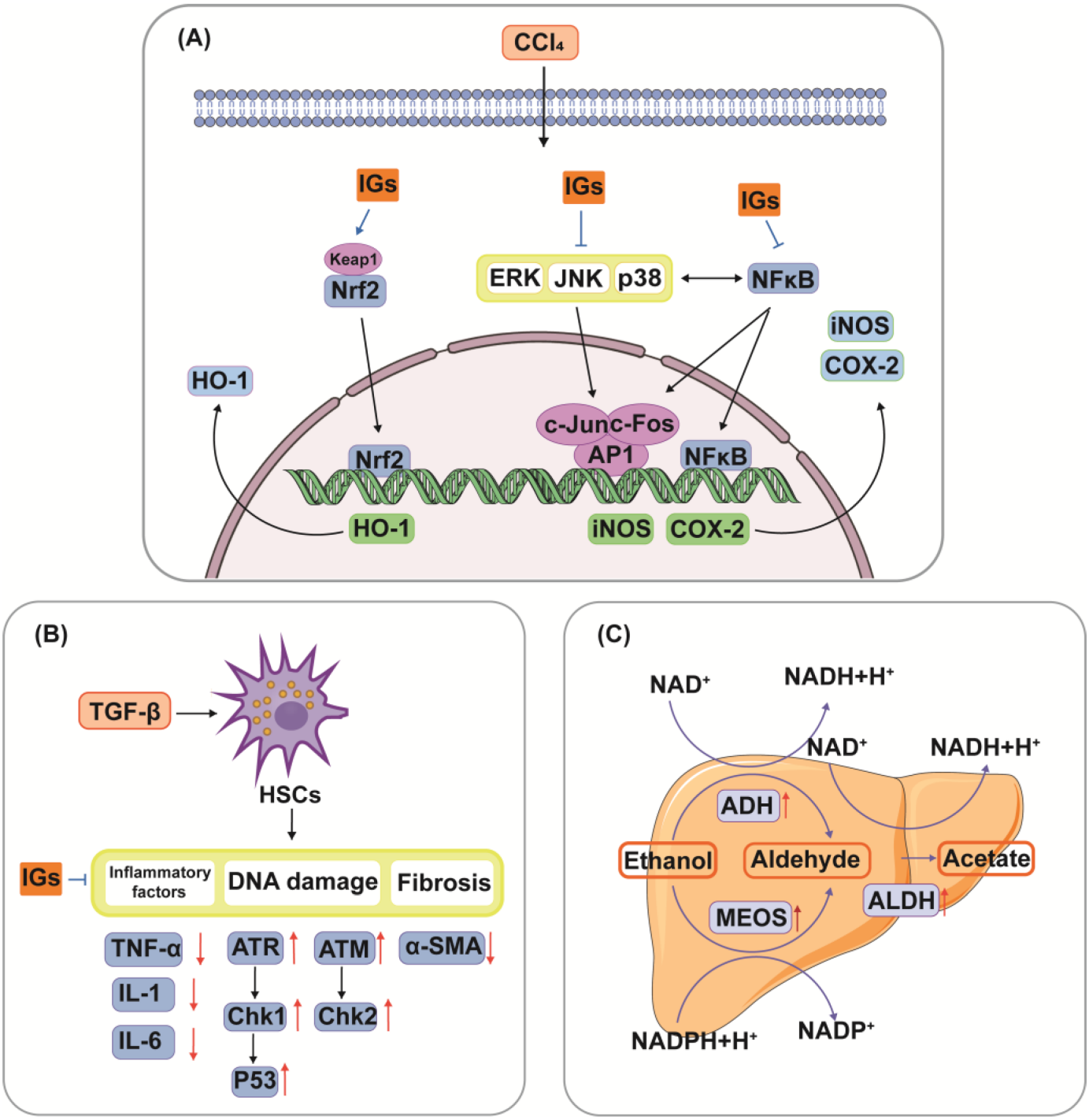

Figure 5. Hepatoprotective mechanism of IGs. Networks of molecular signaling underlying anti-oxidative stress and anti-inflammatory effects of IGs in CCl_4-induced hepatic damage(**A**). IGs inhibit TGF-β-induced activation of HSCs through the DNA damage pathway (**B**). Hepatic metabolic pathways through which IGs alleviate the adverse effects of ethanol (**C**).

IGs also had an improvement effect on hepatic lipid accumulation. In high-fat diet-fed mice, OFI-E (0.3%, 0.6%) reduced fatty acid synthesis and increased fatty acid oxidation and caused a decrease in hepatic fat accumulation, thereby preventing hepatic steatosis [116]. Isorhamnetin-3-*O*-glucoside (**4**), isorhamnetin, 3,4′-diglucoside (**17**), and

isorhamnetin 3-*O*-β-d-glucopyranosyl-7-*O*-β-d-gentiobioside (**47**) (30 μM) had significant inhibitory effects on sodium oleate-induced triglyceride overloading in HepG2 cells [53]. Furthermore, biochemical and histopathological studies showed that sea buckthorn flavonoids (200 mg/kg, po) significantly improved biomarkers in the serum and liver of tetracycline-induced nonalcoholic fatty liver mice [117].

Zhang G et al. observed that isorhamnetin-3-*O*-β-d-glucopyranoside-7-*O*-α-l-rhamnoside (**20**) (40 μM) exhibited a profound inhibitory effect on the activation of hepatic stellate cells (HSCs) induced by transforming growth factor-β (TGF-β), and decreased the levels of inflammatory factors. It over-regulated the proteins of the DNA damage signaling pathway, including the ataxia telangiectasia mutated gene (ATM), Rad3-related gene (ATR), checkpoint kinase1 (Chk1), checkpoint kinase2 (Chk2), p53, and alpha-smooth muscle actin (α-SMA) (**Figure 5**B) [118]. In addition, the active components of sea buckthorn berry (20 and 40 mg/kg) had inhibitory effects on the development of fibrosis in rats after bile duct ligation, and they attenuated liver injury and inflammation by downregulating the expression of αSMA, while over-regulating the DNA damage signaling pathways and their related genes.

Isorhamnetin 3-*O*-β-d-glucopyranoside (**4**) alleviated the adverse effect of ethanol ingestion by enhancing the activities of alcohol dehydrogenase (ADH), the microsomal ethanol oxidizing system (MEOS), and aldehyde dehydrogenase (ALDH) in a hepatic alcohol-metabolizing enzyme system in rats (**Figure 5**C) [119]. In addition, sea buckthorn fermentation liquid (1.75, 2.675, 5.35 g/kg) protected against alcoholic liver disease and modulated the composition of the gut microbiota. It lowered ALT, AST, TNF-α, MDA, and IL-6, while modulating the gut microbiota composition [120].

5.5. Antidiabetic Activity

The antidiabetic properties of IGs may appear through different functions. IGs inhibit various pathways associated with the progression of diabetes, including the regulation of glucose metabolism and enhancing insulin secretion [121].

IGs exert inhibitory activity on several enzymes involved in diabetes management. In the small intestine, IGs inhibit the activity of α-amylase and α-glucosidase, thereby reducing the conversion of dietary saccharides into easily absorbed monosaccharide, and thus, reducing the postprandial enhancement of blood glucose levels (**Figure 6**). Isorhamnetin-3-*O*-glucoside (**4**) showed a strong ability to bind to α-amylase and α-glucosidase (the IC_{50} values were 0.16 ± 0.06 and 0.09 ± 0.01 μM) [122]. Narcissin (**24**) (IC_{50} = 0.129 mM) could be useful in lowering postprandial blood glucose by inhibiting α-amylase activity [123]. Meanwhile, 24 was a good 15-lipoxygenase (IC_{50} = 45 ± 2 μM) inhibitor [124][125]. Isorhamnetin glucosyl-rhamnosyl-pentoside (50 μg/mL) was reported to exhibit antihyperglycemic activity by inhibiting α-amylase activity [126]. Sea buckthorn aqueous extracts were correlated with lipase/α-amylase inhibitory activity in all phases of a digestion model in vitro, with gastric and intestinal fractions largely inhibiting enzyme activity [127].

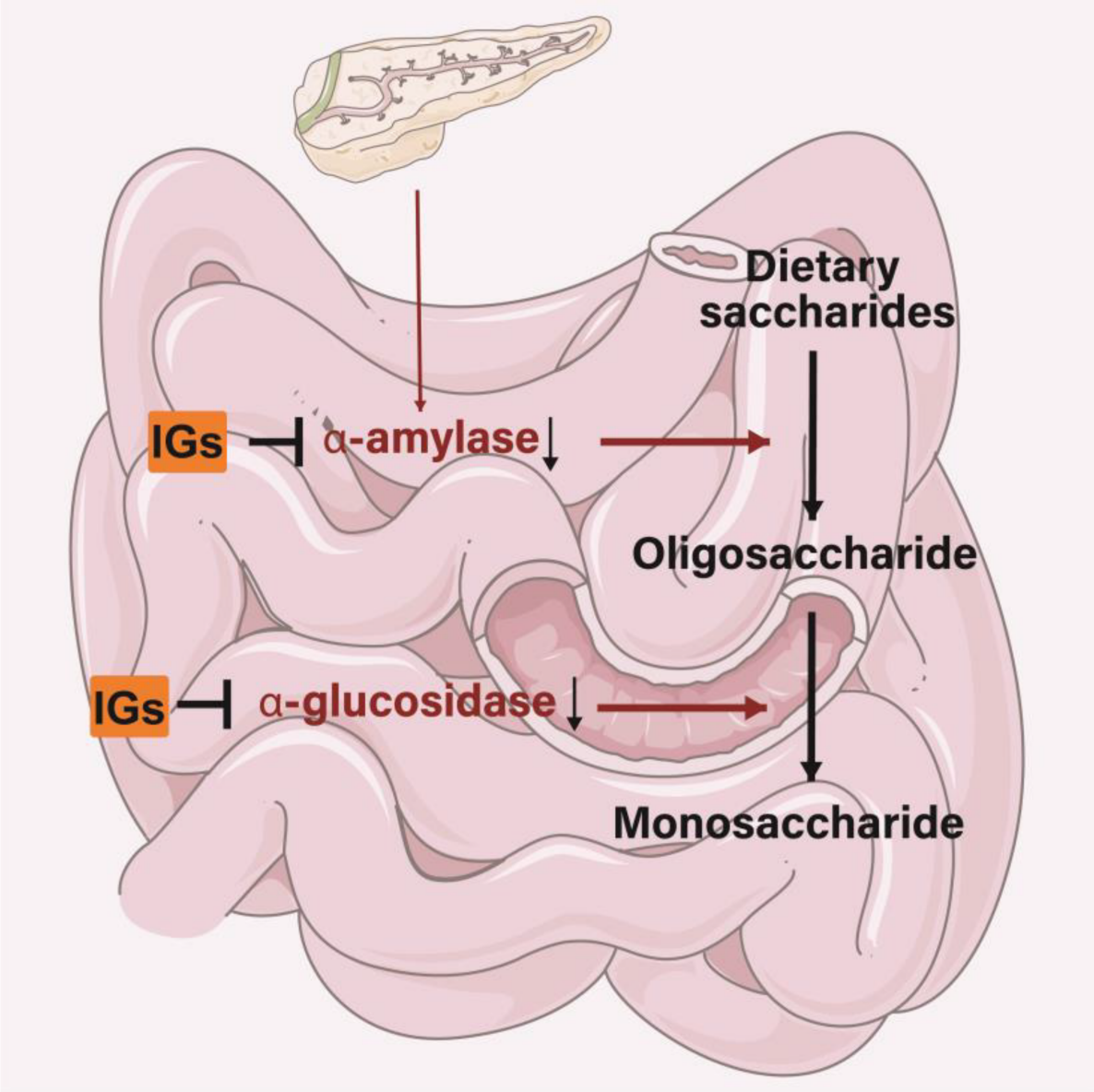

Figure 6. Mechanism of IGs inhibiting α-amylase and α-glucosidase.

5.6. Anti-Obesity Activity

Flavonoids could protect against obesity-related pathology by inhibiting adipogenesis and exerting anti-inflammatory activity [128]. Sea buckthorn leaf extract contains a high content of flavonoid glycosides, especially isorhamnine-3-glucoside (**4**) and quercetin-3-glucoside [129]. Flavonoid glycosides extracted from sea buckthorn leaves (SLGs) could suppress diet-induced obesity in C57BL/6J mice [130]. In this research, the researchers mentioned that 12 weeks of oral administration with a high-fat diet (HFD, 60 kcal% fat) + 0.04% (*w*/*w*) SLGs significantly prevented adiposity and dyslipidemia by suppressing lipogenesis and the absorption of dietary fat. This anti-obesity effect was explained by the improvement of inflammation and a decrease in gluconeogenesis. Narcissin (**24**) and **4** (30 μM) showed moderate inhibitory effects on triglyceride and glycerol-3-phosphate dehydrogenase activity in a 3T3-L1 preadipocyte [131]. Furthermore, it was demonstrated by Chang-Suk Kong et al. that **4** (20 μM) potently suppressed adipogenic differentiation by downregulating peroxisome proliferator-activated

receptor-γ, CCAAT/enhancer-binding proteins, sterol regulatory element-binding protein 1, and the adipocyte-specific proteins in 3T3-L1 preadipocytes. Furthermore, the specific mechanism mediating its action occurred through the activation of AMPK [132].

5.7. Antithrombotic Activity

Thrombosis is a critical event in diseases correlated with atherosclerosis, myocardial infarction, and stroke [133]. The aggregation of platelets at the site of injury, as well as thrombin generation and fibrin formation triggered by the activation of tissue factors, are involved in thrombosis formation [134]. Therefore, the therapeutic mechanism includes the inhibition of platelet activation, adhesion, and aggregation, the improvement of fibrinolytic system function, and the regulation of coagulation system function [135].

5.8. Toxic Effects

Flavonoids are natural components of fruits, vegetables, tea, wine, traditional medicines (such as *ginkgo biloba*), and a considerable number of herbal dietary supplements. With growing interest in alternative medicine, the general population is consuming more flavonoids [136]. Since flavonoids are common edible ingredients in our daily diets, research on their potential cytotoxicity is warranted.

Currently, there are no systematic toxicological studies on IGs, and further studies are needed. Bee bread (BB) is a fermented mixture of plant pollen, honey, and bee saliva, and is rich in flavonoid glycoside derivatives [137]. Filipa Sobral et al. collected a variety of BB samples, and the most abundant compounds in BB1 (>400 µg/mL) were isrohamnetin-*O*-hexosyl-*O*-rutinoside and isorhamnetin-*O*-pentosyl-hexoside. They found that the BB1 sample showed no toxicity to non-tumor porcine liver primary cells [138]. Isorhamnetin-3-rutinoside-4′-glucoside (**35**), isolated from *P. lanceolata* inflorescences, showed significantly less cytotoxicity towards the nontumorigenic cell line MCF-12A at a concentration of 400 µM [139]. Isorhamnetin-3-*O*-β-d-galactopyranoside (**8**) and isorhamnetin-3-*O*-β-d-glucopyranoside (**4**) (100 µg/mL) isolated from *Salsola imbricata Forssk.* exhibited no cytotoxicity in RAW 264.7 macrophage cells [140]. Furthermore, it was demonstrated that the viability of PBMCs was slightly decreased after 48 h of incubation with isoretin-3-*O*-rutin (**24**) (0–180 µM) from *Cyrtosperma johnstonii*. However, the decrease in cell viability was no greater than 30% [141]. A brine shrimp toxicity assay of extracts and isolated compounds from *Terminalia macroptera* leaves showed that narcissin (**24**) was not toxic against brine shrimp larvae at the tested concentrations (200 µM) [124].

6. Bioaccessibility of IGs

The bioaccessibility of bioactive compounds refers to the maximum fraction of the compound released from the food matrix into the lumen of the gastrointestinal tract to be absorbed [142]. Most flavonoids exist in nature as glycosides, in which sugar residues modify the absorption mechanism and their ability to enter cells or interact with transporters and cellular lipoproteins [143][144]. Flavonoid glycosides exhibit better bioavailability both in vitro and in vivo, which is probably due to their higher aqueous solubility and stability during digestion [8]. At the same time, the

gut microbiota plays an important role in improving the bioavailability and enhancing the absorption of flavonoids [145]. The deglycosylation of flavonoid glycosides by the gut microbiota enhances the bioavailability of flavonoids [146].

Compared with isorhamnetin aglycone, IGs have higher accessibility. Antunes-Ricardo et al. found that glycosylation protected isorhamnetin from degradation during simulated digestion, and IGs were better retained in the circulatory system than aglycone [8]. Isorhamnetin-3-*O*-rutinoside (**24**) (93.2 ± 0.2%) and isorhamnetin 3-*O*-glucoside (**4**) (66.8 ± 1.7%) from almond skins showed higher bioaccessibility than isorhamnetin (25.1 ± 7.0%) after simulated digestion [147]. Isorhamnetin glucosyl-rhamnosyl-rhamnoside, isorhamnetin glucosyl-rhamnosyl-pentoside, isorhamnetin hexosyl-hexosyl-pentoside, and isorhamnetin glucosyl-pentoside showed high bioaccessibility in the peels of four prickly pear varieties during in vitro simulated gastrointestinal digestion [148]. Isorhamnetin glucosyl-rhamnosyl-rhamnoside and isorhamnetin glucosyl-pentoside in *Opuntia ficus-indica* cladodes showed bioaccessibility values of 58% and 38% [149].

It was also reported that the antidiabetic, anti-inflammatory, and antiallergic activities of flavonoid glycosides were similar or even higher than those of aglycones when provided orally [150][151][152][153]. The effect of flavonoid glycosides is beneficial, probably due to the fact that flavonoid glycosides maintain higher plasma concentrations and have a longer mean residence time in the blood than aglycones [154]. Typhaneoside (**45**) and isorhamnetin-3-*O*-neohesperidoside (**15**) were detected immediately after the oral administrations of pollen typhae extract in rats, indicating that they were rapidly absorbed after oral administration [155][156]. IGs in sea buckthorn berries were monoglucuronidated in humans and were readily bioavailable [157]. Following the ingestion of lightly fried onions, flavonols were absorbed into the plasma of humans as glycosides, with a higher accumulation of isorhamnetin-4′-glucoside (**9**) in the plasma and urine than quercetin conjugates, which indicated that 9 may be preferentially absorbed [158]. Similarly, the results of a randomized crossover supplementation trial in female volunteers showed that 9 underwent significant elevation in the plasma after the ingestion of onion powder [159]. Antunes-Ricardo et al. reported that IGs found naturally in O. ficus-indica have a longer elimination half-life than isorhamnetin, suggesting that they can maintain constant plasma concentrations, and thus, prolong their biological effects [8].

Planar lipophilic polyphenols, such as curcumin, epigallocatechin gallate, quercetin, and genistein, are known as Pan-Assay Interference Compounds (PAINS) or Invalid Metabolic Panaceas (IMPS) because of their ability to interfere with membrane dipole potential [160]. Ana Marta de Matos et al. demonstrated that compounds produced via *C*-glycosylation are no longer able to alter the membrane dipole potential [161]. However, *O*-glycosylated compounds are easily hydrolyzed in the gut, so they are not suitable for this strategy. There are no more studies on the interference of isorhamnetin glycosides on membrane dipole potential, so further research in this field is warranted.

References

1. Monjotin, N.; Amiot, M.; Fleurentin, J.; Morel, J.; Raynal, S. Clinical Evidence of the Benefits of Phytonutrients in Human Healthcare. Nutrients 2022, 14, 1712.
2. Valente, I.; Cabrita, A.; Malushi, N.; Oliveira, H.; Papa, L.; Rodrigues, J.; Fonseca, A.; Maia, M. Unravelling the phytonutrients and antioxidant properties of European Vicia faba L. seeds. Food Res. Int. 2019, 116, 888–896.
3. Saraei, R.; Marofi, F.; Naimi, A.; Talebi, M.; Ghaebi, M.; Javan, N.; Salimi, O.; Hassanzadeh, A. Leukemia therapy by flavonoids: Future and involved mechanisms. J. Cell. Physiol. 2018, 234, 8203–8220.
4. Roche, A.; Ross, E.; Walsh, N.; O'Donnell, K.; Williams, A.; Klapp, M.; Fullard, N.; Edelstein, S. Representative literature on the phytonutrients category: Phenolic acids. Crit. Rev. Food Sci. Nutr. 2017, 57, 1089–1096.
5. Zhou, D.; Bai, Z.S.; Guo, T.T.; Li, J.Y.; Li, Y.W.; Hou, Y.; Chen, G.; Li, N. Dietary flavonoids and human top-ranked diseases: The perspective of in vivo bioactivity and bioavailability. Trends Food Sci. Technol. 2022, 120, 374–386.
6. Ross, J.A.; Kasum, C.M. Dietary flavonoids: Bioavailability, metabolic effects, and safety. Annu. Rev. Nutr. 2002, 22, 19–34.
7. Tao, H.; Li, L.; He, Y.; Zhang, X.; Zhao, Y.; Wang, Q.; Hong, G. Flavonoids in vegetables: Improvement of dietary flavonoids by metabolic engineering to promote health. Crit. Rev. Food Sci. Nutr. 2022.
8. Marilena, A.R.; César, R.-R.; Janet, G.-U.; Eduardo, C.C.E.; Sergio, S.-S. Bioaccessibility, Intestinal Permeability and Plasma Stability of Isorhamnetin Glycosides from Opuntia ficus-indica (L.). Int. J. Mol. Sci. 2017, 18, 1816.
9. Wang, L.; Fan, X.; Jian, Y.; Dong, M.; Yang, Q.; Meng, D.; Fu, Y. A sensitive and selective multiple reaction monitoring mass spectrometry method for simultaneous quantification of flavonol glycoside, terpene lactones, and biflavonoids in Ginkgo biloba leaves. J. Pharm. Biomed. Anal. 2019, 170, 335–340.
10. Ma, X.; Laaksonen, O.; Zheng, J.; Yang, W.; Trépanier, M.; Kallio, H.; Yang, B. Flavonol glycosides in berries of two major subspecies of sea buckthorn (Hippophaë rhamnoides L.) and influence of growth sites. Food Chem. 2016, 200, 189–198.
11. Hyun, S.; Jung, Y.; Chung, H.; Jung, H.; Choi, J. Isorhamnetin glycosides with free radical and ONOO-scavenging activities from the stamens of Nelumbo nucifera. Arch. Pharmacal. Res. 2006, 29, 287–292.
12. Abdel Motaal, A.; Salem, H.; Almaghaslah, D.; Alsayari, A.; Bin Muhsinah, A.; Alfaifi, M.; Elbehairi, S.; Shati, A.; El-Askary, H. Flavonol Glycosides: In Vitro Inhibition of DPPIV, Aldose Reductase

and Combating Oxidative Stress are Potential Mechanisms for Mediating the Antidiabetic Activity of Cleome droserifolia. Molecules 2020, 25, 5864.

13. Cho, J.; Song, N.; Nam, T.; Shrestha, S.; Park, H.; Lyu, H.; Kim, D.; Lee, G.; Woo, Y.; Jeong, T.; et al. Flavonoids from the grains of C1/R-S transgenic rice, the transgenic Oryza sativa spp. japonica, and their radical scavenging activities. J. Agric. Food Chem. 2013, 61, 10354–10359.
14. Ku, S.K.; Han, M.S.; Bae, J.S. Down-regulation of endothelial protein C receptor shedding by persicarin and isorhamnetin-3-O-galactoside. Thromb. Res. 2013, 132, e58–e63.
15. Antunes-Ricardo, M.; Hernández-Reyes, A.; Uscanga-Palomeque, A.C.; Rodríguez-Padilla, C.; Martínez-Torres, A.C.; Gutiérrez-Uribe, J.A. Isorhamnetin glycoside isolated from Opuntia ficus-indica (L.) MilI induces apoptosis in human colon cancer cells through mitochondrial damage. Chem. Biol. Interact. 2019, 310, 108734.
16. Kim, D.W.; Cho, H.I.; Kim, K.M.; Kim, S.J.; Choi, J.S.; Kim, Y.S.; Lee, S.M. Isorhamnetin-3-O-galactoside Protects against CCl4-Induced Hepatic Injury in Mice. Biomol. Ther. 2012, 20, 406–412.
17. Hussain, H.; Green, I.; Abbas, G.; Adekenov, S.; Hussain, W.; Ali, I. Protein tyrosine phosphatase 1B (PTP1B) inhibitors as potential anti-diabetes agents: Patent review (2015–2018). Expert Opin. Ther. Pat. 2019, 29, 689–702.
18. Barba, F.J.; Garcia, C.; Fessard, A.; Munekata, P.E.S.; Lorenzo, J.M.; Aboudia, A.; Ouadia, A.; Remize, F. Opuntia Ficus Indica Edible Parts: A Food and Nutritional Security Perspective. Food Rev. Int. 2022, 38, 930–952.
19. Wang, K.; Xu, Z.; Liao, X. Bioactive compounds, health benefits and functional food products of sea buckthorn: A review. Crit. Rev. Food Sci. Nutr. 2022, 62, 6761–6782.
20. Ciesarova, Z.; Murkovic, M.; Cejpek, K.; Kreps, F.; Tobolkova, B.; Koplik, R.; Belajova, E.; Kukurova, K.; Dasko, L.; Panovska, Z.; et al. Why is sea buckthorn (Hippophae rhamnoides L.) so exceptional? A review. Food Res. Int. 2020, 133, 109170.
21. Yang, M.C.; Choi, S.Z.; Lee, S.O.; Chung, A.K.; Nam, J.H.; Lee, K.H.; Lee, K.R. Flavonoid constituents and their antioxidant activity of Laportea bulbifera Weddell. Saengyak Hakhoechi 2003, 34, 18–24.
22. Jia, Z.; Zhu, G.; Wang, J. Flavonoid constituents of the seeds of Nitraria tangutorum Bolor. Lanzhou Daxue Xuebao Ziran Kexueban 1991, 27, 102.
23. Park, Y.-K.; Lee, C.Y. Identification of Isorhamnetin 4’-Glucoside in Onions. J. Agric. Food Chem. 1996, 44, 34.
24. Fattorusso, E.; Iorizzi, M.; Lanzotti, V.; Taglialatela-Scafati, O. Chemical composition of shallot (Allium ascalonicum Hort.). J. Agric. Food Chem. 2002, 50, 5686–5690.

25. Kassem, M.E.S.; Afifi, M.S.; Marzouk, M.M.; Mostafa, M.A. Two new flavonol glycosides and biological activities of Diplotaxis harra (Forssk.) Boiss. Nat. Prod. Res. 2013, 27, 2272–2280.
26. Aquino, R.; Behar, I.; D'Agostino, M.; De Simone, F.; Schettino, O.; Pizza, C. Phytochemical investigation on Mercurialis annua. Biochem. Syst. Ecol. 1987, 15, 667.
27. Bechlem, H.; Mencherini, T.; Bouheroum, M.; Benayache, S.; Cotugno, R.; Braca, A.; De Tommasi, N. New Constituents from Gymnocarpos decander. Planta Med. 2017, 83, 1200–1206.
28. Batyuk, V.S.; Vasil'chenko, E.A.; Kovaleva, S.N. Flavonoids of Solidago virgaurea L. and S. canadensis L. and their pharmacological properties. Rastit. Resur. 1988, 24, 92.
29. Litvinenko, V.I.; Bubenchikova, V.N. Phytochemical study of Centaurea cyanus. Chem. Nat. Compd. 1988, 792, 672–674.
30. Oksuz, S.; Putun, E. Flavonoids of Centaurea kotschyi var. kotschyi. Doga: Kim. Ser. 1987, 11, 66–71.
31. Singh, K.N.; Pandey, V.B. Isorhamnetin 7-glucoside from Cnicus wallichi. Phytochemistry 1986, 25, 2683.
32. Butayarov, A.V.; Batirov, E.K.; Tadzhibaev, M.M.; Melibaev, S.; Malikov, V.M. Flavonoids from aerial parts of Russowia sogdiana. Chem. Nat. Compd. 1993, 29, 807–808.
33. Abdala, L.R. Flavonoids of the aerial parts from Tagetes lucida (Asteraceae). Biochem. Syst. Ecol. 1999, 27, 753–754.
34. He, A.; Wang, M. Flavonoids from stringy stonecrop (Sedum sarmentosum). Zhongcaoyao 1997, 28, 517–522.
35. Grace, M.H.; Mohamed, T.K.; Khattab, A.M. Flavonoids of Carduncellus eriocephalus. Egypt. J. Pharm. Sci. 1999, 39, 409–416.
36. Zhang, Z.-x.; Zhang, J.; Luo, J.-q.; Zhang, T.-h. Chemical constituents of the seeds of Atriplex centralasiatica. Shenyang Yaoke Daxue Xuebao 2008, 25, 708–710.
37. Awaad, A.S.; Grace, M.H. Flavonoids and pharmacological activity of Vernonia galamensis ssp. galamensis var. petitiana (A. Rich) M. Gilbert. Egypt. J. Pharm. Sci. 2001, 40, 117–128.
38. Krzeminski, K.; Krzeminska, K. Flavonoid heterosides in the herb of Raphanus raphanistrum L. Herba Pol. 1977, 23, 291.
39. Zhang, S.; Shi, J.; Sun, Z.; Hu, C. Studies on chemical constituents from Caragana intermedia. Zhongyaocai 2006, 29, 19–21.
40. Paskhov, D.; Marichkova, L. Flavonoids of Astragalus centralpinus and their effect on the smooth muscle of the gastrointestinal tract. Probl. Farm. 1983, 11, 36–42.

41. Christensen, L.P.; Kaack, K.; Frette, X.C. Selection of elderberry (Sambucus nigra L.) genotypes best suited for the preparation of elderflower extracts rich in flavonoids and phenolic acids. Eur. Food Res. Technol. 2008, 227, 293–305.
42. Vidal-Ollivier, E.; Elias, R.; Faure, F.; Babadjamian, A.; Crespin, F.; Balansard, G.; Boudon, G. Flavonol glycosides from Calendula officinalis flowers. Planta Med. 1989, 55, 73.
43. Merfort, I.; Wendisch, D. Flavonoid glucuronides from the flowers of Arnica montana. Planta Med. 1988, 54, 247.
44. Kim, S.Y.; Park, J.Y.; Park, P.S.; Bang, S.H.; Lee, K.M.; Lee, Y.R.; Jang, Y.H.; Kim, M.J.; Chun, W.; Heo, M.Y.; et al. Flavonoid glycosides as acetylcholinesterase inhibitors from the whole plants of Persicaria thunbergii. Nat. Prod. Sci. 2014, 20, 191–195.
45. Mezache, N.; Derbre, S.; Akkal, S.; Laouer, H.; Seraphin, D.; Richomme, P. Fast counter current chromatography of n-butanolic fraction from Senecio giganteus (Asteraceae). Nat. Prod. Commun. 2009, 4, 1357–1362.
46. Granica, S.; Czerwinska, M.E.; Zyzynska-Granica, B.; Kiss, A.K. Antioxidant and anti-inflammatory flavonol glucuronides from Polygonum aviculare L. Fitoterapia 2013, 91, 180–188.
47. Cheng, W.; Sui, C.; Yuan, J.; Zhang, H. Flavonoids of argun groundsel (Senecio argunensis). Zhongcaoyao 1999, 30, 727–729.
48. Zaki, A.A.; Xu, X.; Wang, Y.; Shie, P.-H.; Qiu, L. A new anti-inflammatory flavonoid glycoside from Tetraena aegyptia. Nat. Prod. Res. 2021, 35, 1985–1990.
49. Cheng, J.; Wu, J.; Azi, g.; Li, R.; Lin, G. Chemical constituents of Aertaihuanqi (Astragalus altaicus). Zhongcaoyao 1994, 25, 563.
50. Saleh, N.A.M.; Mansour, R.M.A.; Markham, K.R. An acylated isorhamnetin glycoside from Aerva javanica. Phytochemistry 1990, 29, 1344.
51. Jia, S.; Liu, Y.; Ma, C.; Yang, S.; Zhou, H.; Zhao, D.; Liu, D.; Li, S. Flavonoid constituents of the pollen of Typha angustfolia L. (Puhuang). Yaoxue Xuebao 1986, 21, 441.
52. Olszewska, M.A.; Kwapisz, A. Metabolite profiling and antioxidant activity of Prunus padus L. flowers and leaves. Nat. Prod. Res. 2011, 25, 1115–1131.
53. Wang, S.; Shi, P.; Qu, L.; Ruan, J.; Yang, S.; Yu, H.; Zhang, Y.; Wang, T. Bioactive constituents obtained from the seeds of Lepidium apetalum willd. Molecules 2017, 22, 540.
54. Hoerhammer, L.; Wagner, H.; Kraemer, H.; Farkas, L. Isorhamnetin glycosides. II. Isolation and composition of new glycosides from Brassica napus and Sinapis arvensis. Chem. Ber. 1967, 100, 2301.

55. Halim, A.F.; Saad, H.-E.A.; Hashish, N.E. Flavonol glycosides from Nitraria retusa. Phytochemistry 1995, 40, 349.

56. Tang, Y.; Lou, F.; Wang, J.; Li, Y.; Zhuang, S. Coumaroyl flavonol glycosides from the leaves of Ginkgo biloba. Phytochemistry 2001, 58, 1251–1256.

57. Wang, D.-M.; Pu, W.-J.; Wang, Y.-H.; Zhang, Y.-J.; Wang, S.-S. A new isorhamnetin glycoside and other phenolic compounds from Callianthemum taipaicum. Molecules 2012, 17, 4595–4603.

58. Schoensiegel, I.; Egger, K. Flavonol glycosides in the petals of Narcissus pseudonarcissus. Z. Naturforsch. B 1969, 24, 1215.

59. Zhang, Z.-l.; Cai, M.-t.; Zuo, Y.-m.; Wang, Y.-y. Studies on chemical constituents in fruits of Trillium tschonoskii Maxim. Shizhen Guoyi Guoyao 2014, 25, 541–543.

60. Yoshitama, K.; Shida, Y.; Oyamada, T.; Takasaki, N.; Yahara, S. "Studies of the flavonoids of the genus Trillium". 3. Flavonol glycosides in the leaves of Trillium apetalon Makino and T. kamtschaticum Pallas. J. Plant Res. 1997, 110, 443–448.

61. Rodriguez, E.; Shen, M.C.; Mabry, T.J.; Dominguez, X.A. Isorhamnetin 3-0-glucoside 7-0-arabinoside from Eschscholzia mexicana. Phytochemistry 1973, 12, 2069.

62. Li, H.; Kim, U.H.; Yoon, J.H.; Ji, H.S.; Park, H.M.; Park, H.Y.; Jeong, T.S. Suppression of Hyperglycemia and Hepatic Steatosis by Black-Soybean-Leaf Extract via Enhanced Adiponectin-Receptor Signaling and AMPK Activation. J. Agric. Food Chem. 2019, 67, 90–101.

63. Kijima, H.; Ide, T.; Otsuka, H.; Takeda, Y. Alangiflavoside, a new flavonol glycoside from the leaves of Alangium premnifolium. J. Nat. Prod. 1995, 58, 1753.

64. Yasukawa, K.; Sekine, H.; Takido, M. Studies of the constituents of genus Lysimachia. Part 4. Two flavonol glycosides from Lysimachia fortunei. Phytochemistry 1989, 28, 2215.

65. Liu, H.; Mou, Y.; Zhao, J.; Wang, J.; Zhou, L.; Wang, M.; Wang, D.; Han, J.; Yu, Z.; Yang, F. Flavonoids from Halostachys caspica and their antimicrobial and antioxidant activities. Molecules 2010, 15, 7933–7945.

66. Kaouadji, M.; Doucoure, A.; Mariotte, A.M.; Chulia, A.J.; Thomasson, F. Flavonol triglycosides from Blackstonia perfoliata. Phytochemistry 1990, 29, 1283.

67. El-Sayed, N.H.; Abu Dooh, A.M.; El-Khrisy, E.A.M.; Mabry, T.J. Flavonoids of Cassia italica. Phytochemistry 1992, 31, 2187.

68. Trineeva, O.V.; Perova, I.B.; Slivkin, A.I.; Eller, K.I. Study the composition of flavonoids fruits of sea buckthorn. Sorbtsionnye Khromatogr. Protsessy 2017, 17, 87–93.

69. Skalski, B.; Lis, B.; Pecio, L.; Kontek, B.; Olas, B.; Zuchowski, J.; Stochmal, A. Isorhamnetin and its new derivatives isolated from sea buckthorn berries prevent H(2)O(2)/Fe—Induced oxidative

stress and changes in hemostasis. Food Chem. Toxicol. 2019, 125, 614–620.

70. Speisky, H.; Shahidi, F.; Costa de Camargo, A.; Fuentes, J. Revisiting the Oxidation of Flavonoids: Loss, Conservation or Enhancement of Their Antioxidant Properties. Antioxidants 2022, 11, 133.
71. Choi, J.; Jung, M.; Park, H.; Chung, H.; Kang, S. Further isolation of peroxynitrite and 1,1-diphenyl-2-picrylhydrazyl radical scavenging isorhamnetin 7-O-glucoside from the leaves of Brassica juncea L. Arch. Pharmacal Res. 2002, 25, 625–627.
72. Hawas, U.; Abou El-Kassem, L.; Shaher, F.; Al-Farawati, R. In vitro inhibition of Hepatitis C virus protease and antioxidant by flavonoid glycosides from the Saudi costal plant. Nat. Prod. Res. 2019, 33, 3364–3371.
73. Chen, P.; Cao, Y.; Bao, B.; Zhang, L.; Ding, A. Antioxidant capacity of Typha angustifolia extracts and two active flavonoids. Pharm. Biol. 2017, 55, 1283–1288.
74. Yang, C.; Yang, Y.; Aisa, H.A.; Xin, X.; Ma, H.; Yili, A.; Zhao, Y. Bioassay-guided isolation of antioxidants from Astragalus altaicus by combination of chromatographic techniques. J. Sep. Sci. 2012, 35, 977–983.
75. Qi, J.; Gui, X.; Chen, G. Research on active component extraction of nitraria sibirica pall. fruit and their antioxidant activity. Mod. Chin. Med. 2013, 15, 827–831.
76. Bouhlel, I.; Limem, I.; Skandrani, I.; Nefatti, A.; Ghedira, K.; Dijoux-Franca, M.; Leila, C. Assessment of isorhamnetin 3-O-neohesperidoside from Acacia salicina: Protective effects toward oxidation damage and genotoxicity induced by aflatoxin B1 and nifuroxazide. J. Appl. Toxicol. JAT 2010, 30, 551–558.
77. Demirkiran, O.; Sabudak, T.; Ozturk, M.; Topcu, G. Antioxidant and tyrosinase inhibitory activities of flavonoids from Trifolium nigrescens Subsp. petrisavi. J. Agric. Food Chem. 2013, 61, 12598–12603.
78. Hassan, R.; Tawfik, W.; Abou-Setta, L. The flavonoid constituents of Leucaena leucocephala. Growing in Egypt, and their biological activity. Afr. J. Tradit. Complement. Altern. Med. AJTCAM 2014, 11, 67–72.
79. Yuca, H.; Özbek, H.; Demirezer, L.; Kasil, H.G.; Güvenalp, Z. trans-Tiliroside: A potent α-glucosidase inhibitor from the leaves of Elaeagnus angustifolia L. Phytochemistry 2021, 188, 112795.
80. Li, Y.; Guo, S.; Zhu, Y.; Yan, H.; Qian, D.W.; Wang, H.Q.; Yu, J.Q.; Duan, J.A. Flowers of Astragalus membranaceus var. mongholicus as a Novel High Potential By-Product: Phytochemical Characterization and Antioxidant Activity. Molecules 2019, 24, 434.

81. Yokozawa, T.; Kim, H.; Cho, E.; Choi, J.; Chung, H. Antioxidant effects of isorhamnetin 3,7-di-O-beta-d-glucopyranoside isolated from mustard leaf (Brassica juncea) in rats with streptozotocin-induced diabetes. J. Agric. Food Chem. 2002, 50, 5490–5495.
82. Boubaker, J.; Ben Sghaier, M.; Skandrani, I.; Ghedira, K.; Chekir-Ghedira, L. Isorhamnetin 3-O-robinobioside from Nitraria retusa leaves enhance antioxidant and antigenotoxic activity in human chronic myelogenous leukemia cell line K562. BMC Complement. Altern. Med. 2012, 12, 135.
83. Abdallah, H.; Esmat, A. Antioxidant and anti-inflammatory activities of the major phenolics from Zygophyllum simplex L. J. Ethnopharmacol. 2017, 205, 51–56.
84. Bouhlel, I.; Skandrani, I.; Nefatti, A.; Valenti, K.; Ghedira, K.; Mariotte, A.M.; Hininger-Favier, I.; Laporte, F.; Dijoux-Franca, M.G.; Chekir-Ghedira, L. Antigenotoxic and antioxidant activities of isorhamnetin 3-O neohesperidoside from Acacia salicina. Drug Chem. Toxicol. 2009, 32, 258–267.
85. Yeskaliyeva, B.; Mesaik, M.; Abbaskhan, A.; Kulsoom, A.; Burasheva, G.; Abilov, Z.; Choudhary, M.; Atta-ur-Rahman. Bioactive flavonoids and saponins from Climacoptera obtusifolia. Phytochemistry 2006, 67, 2392–2397.
86. Matias, A.; Nunes, S.; Poejo, J.; Mecha, E.; Serra, A.; Madeira, P.; Bronze, M.; Duarte, C. Antioxidant and anti-inflammatory activity of a flavonoid-rich concentrate recovered from Opuntia ficus-indica juice. Food Funct. 2014, 5, 3269–3280.
87. Guo, R.; Guo, X.; Li, T.; Fu, X.; Liu, R. Comparative assessment of phytochemical profiles, antioxidant and antiproliferative activities of Sea buckthorn (Hippophaë rhamnoides L.) berries. Food Chem. 2017, 221, 997–1003.
88. Andersson, U.; Yang, H.; Harris, H. Extracellular HMGB1 as a therapeutic target in inflammatory diseases? Expert Opin. Ther. Targets 2018, 22, 263–277.
89. Kim, T.; Ku, S.; Bae, J. Anti-inflammatory activities of isorhamnetin-3-O-galactoside against HMGB1-induced inflammatory responses in both HUVECs and CLP-induced septic mice. J. Cell. Biochem. 2013, 114, 336–345.
90. Yong, H.; Koh, M.; Moon, A. The p38 MAPK inhibitors for the treatment of inflammatory diseases and cancer. Expert Opin. Investig. Drugs 2009, 18, 1893–1905.
91. Park, J.; Kim, S.; Lee, H.; Kim, S.; Kwon, Y.; Chun, W. Isorhamnetin-3-O-Glucuronide Suppresses JNK and p38 Activation and Increases Heme-Oxygenase-1 in Lipopolysaccharide-Challenged RAW264.7 Cells. Drug Dev. Res. 2016, 77, 143–151.
92. Ahmed, A.F.; Wen, Z.-H.; Bakheit, A.H.; Basudan, O.A.; Ghabbour, H.A.; Al-Ahmari, A.; Feng, C.-W. A Major Diplotaxis harra-Derived Bioflavonoid Glycoside as a Protective Agent against Chemically Induced Neurotoxicity and Parkinson’s Models; In Silico Target Prediction; and Biphasic HPTLC-Based Quantification. Plants 2022, 11, 648.

93. Fu, Y.; Jia, Y.; Sun, Y.; Liu, X.; Yi, J.; Cai, S. Dietary Flavonoids Alleviate Inflammation and Vascular Endothelial Barrier Dysfunction Induced by Advanced Glycation End Products In Vitro. Nutrients 2022, 14, 1026.
94. Jin, H.; Ko, H.; Chowdhury, M.; Lee, D.; Woo, E. A new indole glycoside from the seeds of Raphanus sativus. Arch. Pharmacal Res. 2016, 39, 755–761.
95. Osman, S.; El Kashak, W.; Wink, M.; El Raey, M. New Isorhamnetin Derivatives from Salsola imbricata Forssk. Leaves with Distinct Anti-inflammatory Activity. Pharmacogn. Mag. 2016, 12, S47–S51.
96. Ameur, A.S.; Negab, I.; Zouzou, F.; Legseir, B. Anti-inflammatory and antispasmodic activities of isorhamnetin glycosides isolated from Opuntia ficus-indica (L.) mill. Flowers. Res. J. Pharm. Biol. Chem. Sci. 2016, 7, 432–437.
97. Antunes-Ricardo, M.; Gutiérrez-Uribe, J.; Martínez-Vitela, C.; Serna-Saldívar, S. Topical anti-inflammatory effects of isorhamnetin glycosides isolated from Opuntia ficus-indica. BioMed Res. Int. 2015, 2015, 847320.
98. Ren, Q.-C.; Li, X.-H.; Li, Q.-Y.; Yang, H.-L.; Wang, H.-L.; Zhang, H.; Zhao, L.; Jiang-Yong, S.-L.; Meng, X.-L.; Zhang, Y.; et al. Total flavonoids from sea buckthorn ameliorates lipopolysaccharide/cig arette smoke-induced airway inflammation. Phytother. Res. PTR 2019, 33, 2102–2117.
99. Raffa, D.; Maggio, B.; Raimondi, M.; Plescia, F.; Daidone, G. Recent discoveries of anticancer flavonoids. Eur. J. Med. Chem. 2017, 142, 213–228.
100. Mohammed, M.; El-Sharkawy, E.R.; Matloub, A.A. Cytotoxic flavonoids from Diplotaxis harra (Forssk.) Boiss. growing in Sinai. J. Med. Plant Res. 2013, 520, 5099–5103.
101. Tofighi, Z.; Asgharian, P.; Goodarzi, S.; Hadjiakhoondi, A.; Ostad, S.N.; Yassa, N. Potent cytotoxic flavonoids from Iranian Secur. Securidaca. Med. Chem. Res. 2014, 23, 1718–1724.
102. Tundis, R.; Loizzo, M.; Bonesi, M.; Menichini, F.; Statti, G.; Menichini, F. In vitro cytotoxic activity of Salsola oppositifolia Desf. (Amaranthaceae) in a panel of tumour cell lines. Z. Fur Naturforschung. C J. Biosci. 2008, 63, 347–354.
103. Liu, Y.; Xiao, Z.Y.; Liu, P.; Huang, J.; Algradi, A.M.; Pan, J.; Guan, W.; Zhou, Y.Y.; Yang, B.Y.; Kuang, H.X. New flavonoids from the aerial part of Bupleurum chinense DC. Fitoterapia 2020, 147, 104739.
104. Pfeffer, C.; Singh, A. Apoptosis: A Target for Anticancer Therapy. Int. J. Mol. Sci. 2018, 19, 448.
105. Yao, N.; Li, Y.; Lei, Y.; Hu, N.; Chen, W.; Yao, Z.; Yu, M.; Liu, J.; Ye, W.; Zhang, D. A piperazidine derivative of 23-hydroxy betulinic acid induces a mitochondria-derived ROS burst to trigger

apoptotic cell death in hepatocellular carcinoma cells. J. Exp. Clin. Cancer Res. CR 2016, 35, 192.

106. Rademaker, G.; Boumahd, Y.; Peiffer, R.; Anania, S.; Wissocq, T.; Liégeois, M.; Luis, G.; Sounni, N.; Agirman, F.; Maloujahmoum, N.; et al. Myoferlin targeting triggers mitophagy and primes ferroptosis in pancreatic cancer cells. Redox Biol. 2022, 53, 102324.
107. Mendes, S.; Sá, R.; Magalhães, M.; Marques, F.; Sousa, M.; Silva, E. The Role of ROS as a Double-Edged Sword in (In)Fertility: The Impact of Cancer Treatment. Cancers 2022, 14, 1585.
108. Highton, A.; Schuster, I.; Degli-Esposti, M.; Altfeld, M. The role of natural killer cells in liver inflammation. Semin. Immunopathol. 2021, 43, 519–533.
109. Lücke, J.; Sabihi, M.; Zhang, T.; Bauditz, L.; Shiri, A.; Giannou, A.; Huber, S. The good and the bad about separation anxiety: Roles of IL-22 and IL-22BP in liver pathologies. Semin. Immunopathol. 2021, 43, 591–607.
110. Sayed, A.M.; Hassanein, E.; Hassan, S.; Hussein, O.E.; Mahmoud, A.M. Flavonoids-mediated SIRT1 signaling activation in hepatic disorders. Life Sci. 2020, 259, 118173.
111. Igarashi, K.; Mikami, T.; Takahashi, Y.; Sato, H. Comparison of the preventive activity of isorhamnetin glycosides from atsumi-kabu (red turnip, Brassica, campestris L.) leaves on carbon tetrachloride-induced liver injury in mice. Biosci. Biotechnol. Biochem. 2008, 72, 856–860.
112. Galati, E.; Mondello, M.; Lauriano, E.; Taviano, M.; Galluzzo, M.; Miceli, N. Opuntia ficus indica (L.) Mill. fruit juice protects liver from carbon tetrachloride-induced injury. Phytother. Res. PTR 2005, 19, 796–800.
113. Maheshwari, D.; Yogendra Kumar, M.; Verma, S.; Singh, V.; Singh, S. Antioxidant and hepatoprotective activities of phenolic rich fraction of Seabuckthorn (Hippophae rhamnoides L.) leaves. Food Chem. Toxicol. Int. J. Publ. Br. Ind. Biol. Res. Assoc. 2011, 49, 2422–2428.
114. Kuang, H.; Tang, Z.; Wang, X.; Yang, B.; Wang, Z.; Wang, Q. Chemical constituents from Sambucus williamsii Hance fruits and hepatoprotective effects in mouse hepatocytes. Nat. Prod. Res. 2018, 32, 2008–2016.
115. Ben Saad, A.; Dalel, B.; Rjeibi, I.; Smida, A.; Ncib, S.; Zouari, N.; Zourgui, L. Phytochemical, antioxidant and protective effect of cactus cladodes extract against lithium-induced liver injury in rats. Pharm. Biol. 2017, 55, 516–525.
116. Rodríguez-Rodríguez, C.; Torres, N.; Gutiérrez-Uribe, J.; Noriega, L.; Torre-Villalvazo, I.; Leal-Díaz, A.; Antunes-Ricardo, M.; Márquez-Mota, C.; Ordaz, G.; Chavez-Santoscoy, R.; et al. The effect of isorhamnetin glycosides extracted from Opuntia ficus-indica in a mouse model of diet induced obesity. Food Funct. 2015, 6, 805–815.

117. Guo, Z.; Cheng, J.; Zheng, L.; Xu, W.; Xie, Y. Mechanochemical-Assisted Extraction and Hepatoprotective Activity Research of Flavonoids from Sea Buckthorn (Hippophaë rhamnoides L.) Pomaces. Molecules 2021, 26, 7615.

118. Zhang, G.; Liu, Y.; Liu, P. Active Components from Sea Buckthorn (Hippophae rhamnoides L.) Regulate Hepatic Stellate Cell Activation and Liver Fibrogenesis. J. Agric. Food Chem. 2018, 66, 12257–12264.

119. Hur, J.M.; Park, S.H.; Choi, J.W.; Park, J.C. Effects of extract and isorhamnetin glycoside from Brassica juncea on hepatic alcohol-metabolizing enzyme system in rats. Nat. Prod. Sci. 2012, 18, 190–194.

120. Ran, B.; Guo, C.; Li, W.; Li, W.; Wang, Q.; Qian, J.; Li, H. Sea buckthorn (Hippophae rhamnoides L.) fermentation liquid protects against alcoholic liver disease linked to regulation of liver metabolome and the abundance of gut microbiota. J. Sci. Food Agric. 2021, 101, 2846–2854.

121. Tanveer, A.; Akram, K.; Farooq, U.; Hayat, Z.; Shafi, A. Management of diabetic complications through fruit flavonoids as a natural remedy. Crit. Rev. Food Sci. Nutr. 2017, 57, 1411–1422.

122. Nan, X.; Jia, W.; Zhang, Y.; Wang, H.; Lin, Z.; Chen, S. An on-line detection system for screening small molecule inhibitors of α-Amylase and α-Glucosidase in Prunus mume. J. Chromatogr. A 2022, 1663, 462754.

123. Tundis, R.; Loizzo, M.R.; Statti, G.A.; Menichini, F. Inhibitory effects on the digestive enzyme alpha-amylase of three Salsola species (Chenopodiaceae) in vitro. Pharm. Die 2007, 62, 473–475.

124. Pham, A.T.; Malterud, K.E.; Paulsen, B.S.; Diallo, D.; Wangensteen, H. alpha-Glucosidase inhibition, 15-lipoxygenase inhibition, and brine shrimp toxicity of extracts and isolated compounds from Terminalia macroptera leaves. Pharm. Biol. 2014, 52, 1166–1169.

125. Gómez-Maqueo, A.; García-Cayuela, T.; Fernández-López, R.; Welti-Chanes, J.; Cano, M. Inhibitory potential of prickly pears and their isolated bioactives against digestive enzymes linked to type 2 diabetes and inflammatory response. J. Sci. Food Agric. 2019, 99, 6380–6391.

126. Siegień, J.; Buchholz, T.; Popowski, D.; Granica, S.; Osińska, E.; Melzig, M.; Czerwińska, M. Pancreatic lipase and α-amylase inhibitory activity of extracts from selected plant materials after gastrointestinal digestion in vitro. Food Chem. 2021, 355, 129414.

127. Fujimura, Y.; Watanabe, M.; Morikawa-Ichinose, T.; Fujino, K.; Yamamoto, M.; Nishioka, S.; Inoue, C.; Ogawa, F.; Yonekura, M.; Nakasone, A.; et al. Metabolic Profiling for Evaluating the Dipeptidyl Peptidase-IV Inhibitory Potency of Diverse Green Tea Cultivars and Determining Bioactivity-Related Ingredients and Combinations. J. Agric. Food Chem. 2022, 70, 6455–6466.

128. Kwon, E.; Lee, J.; Kim, Y.; Do, A.; Choi, J.; Cho, S.; Jung, U.; Lee, M.; Park, Y.; Choi, M. Seabuckthorn Leaves Extract and Flavonoid Glycosides Extract from Seabuckthorn Leaves

Ameliorates Adiposity, Hepatic Steatosis, Insulin Resistance, and Inflammation in Diet-Induced Obesity. Nutrients 2017, 9, 569.

129. Tkacz, K.; Wojdyło, A.; Turkiewicz, I.; Ferreres, F.; Moreno, D.; Nowicka, P. UPLC-PDA-Q/TOF-MS profiling of phenolic and carotenoid compounds and their influence on anticholinergic potential for AChE and BuChE inhibition and on-line antioxidant activity of selected Hippophaë rhamnoides L. cultivars. Food Chem. 2020, 309, 125766.
130. Chen, Y.G.; Li, P.; Li, P.; Yan, R.; Zhang, X.Q.; Wang, Y.; Zhang, X.T.; Ye, W.C.; Zhang, Q.W. α-Glucosidase Inhibitory Effect and Simultaneous Quantification of Three Major Flavonoid Glycosides in Microctis folium. Molecules 2013, 18, 4221–4232.
131. Yang, Z.; Wen, X.; Li, Y.; Matsuzaki, K.; Kitanaka, S. Inhibitory effects of the constituents of Hippophae rhamnoides on 3T3-L1 cell differentiation and nitric oxide production in RAW264.7 cells. Chem. Pharm. Bull. 2013, 61, 279–285.
132. Kong, C.S.; Seo, Y. Antiadipogenic activity of isohamnetin 3-O-beta-d-glucopyranoside from Salicornia herbacea. Immunopharmacol. Immunotoxicol. 2012, 34, 907–911.
133. Furie, B.; Furie, B.C. Mechanisms of thrombus formation. N. Engl. J. Med. 2008, 359, 938–949.
134. Furie, B.; Furie, B.C. In vivo thrombus formation. J. Thromb. Haemost. JTH 2007, 5 (Suppl. S1), 12–17.
135. Mega, J.L.; Simon, T. Pharmacology of antithrombotic drugs: An assessment of oral antiplatelet and anticoagulant treatments. Lancet 2015, 386, 281–291.
136. Galati, G.; O'Brien, P.J. Potential toxicity of flavonoids and other dietary phenolics: Significance for their chemopreventive and anticancer properties. Free Radic. Biol. Med. 2004, 37, 287–303.
137. Othman, Z.A.; Zakaria, Z.; Suleiman, J.B.; Che Jalil, N.A.; Wan Ghazali, W.S.; Mohamed, M. Bee bread attenuates the progression of atherosclerosis by activating Nrf2/Keap1 and modulating TNF-alpha/NF-kappabeta-associated mast cell migration and a mitochondrial-dependent apoptotic pathway in the obese rat model. Food Funct. 2022, 13, 8119–8130.
138. Sobral, F.; Calhelha, R.C.; Barros, L.; Duenas, M.; Tomas, A.; Santos-Buelga, C.; Vilas-Boas, M.; Ferreira, I.C. Flavonoid Composition and Antitumor Activity of Bee Bread Collected in Northeast Portugal. Molecules 2017, 22, 248.
139. Budzianowska, A.; Toton, E.; Romaniuk-Drapala, A.; Kikowska, M.; Budzianowski, J. Cytotoxic Effect of Phenylethanoid Glycosides Isolated from Plantago lanceolata L. Life 2023, 13, 556.
140. Wu, Q.; Kroon, P.A.; Shao, H.; Needs, P.W.; Yang, X. Differential Effects of Quercetin and Two of Its Derivatives, Isorhamnetin and Isorhamnetin-3-glucuronide, in Inhibiting the Proliferation of Human Breast-Cancer MCF-7 Cells. J. Agric. Food Chem. 2018, 66, 7181–7189.

141. Naksuriya, O.; Daowtak, K.; Tima, S.; Okonogi, S.; Mueller, M.; Toegel, S.; Khonkarn, R. Hydrolyzed Flavonoids from Cyrtosperma johnstonii with Superior Antioxidant, Antiproliferative, and Anti-Inflammatory Potential for Cancer Prevention. Molecules 2022, 27, 3226.

142. Peanparkdee, M.; Borompichaichartkul, C.; Iwamoto, S. Bioaccessibility and antioxidant activity of phenolic acids, flavonoids, and anthocyanins of encapsulated Thai rice bran extracts during in vitro gastrointestinal digestion. Food Chem. 2021, 361, 130161.

143. Mrudulakumari Vasudevan, U.; Lee, E.Y. Flavonoids, terpenoids, and polyketide antibiotics: Role of glycosylat ion and biocatalytic tactics in engineering glycosylation. Biotechnol. Adv. 2020, 41, 107550.

144. Manach, C.; Williamson, G.; Morand, C.; Scalbert, A.; Remesy, C. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. Am. J. Clin. Nutr. 2005, 81, 230S–242S.

145. Al-Ishaq, R.K.; Liskova, A.; Kubatka, P.; Busselberg, D. Enzymatic Metabolism of Flavonoids by Gut Microbiota and Its Impact on Gastrointestinal Cancer. Cancers 2021, 13, 3934.

146. Yang, B.; Liu, H.L.; Yang, J.L.; Gupta, V.K.; Jiang, Y.M. New insights on bioactivities and biosynthesis of flavonoid glycosides. Trends Food Sci. Technol. 2018, 79, 116–124.

147. Mandalari, G.; Tomaino, A.; Rich, G.T.; Curto, R.L.; Arcoraci, T.; Martorana, M.; Bisignano, C.; Saija, A.; Parker, M.L.; Waldron, K.W.; et al. Polyphenol and nutrient release from skin of almonds during simulated human digestion—ScienceDirect. Food Chem. 2010, 122, 1083–1088.

148. Gómez-Maqueo, A.; Antunes-Ricardo, M.; Welti-Chanes, J.; Cano, M.P. Digestive Stability and Bioaccessibility of Antioxidants in Prickly Pear Fruits from the Canary Islands: Healthy Foods and Ingredients. Antioxidants 2020, 9, 164.

149. De Santiago, E.; Gill, C.I.; Carafa, I.; Tuohy, K.M.; De Peña, M.P.; Cid, C. Digestion and Colonic Fermentation of Raw and Cooked Opuntia ficus-indica Cladodes Impacts Bioaccessibility and Bioactivity. J. Agric. Food Chem. 2019, 67, 2490–2499.

150. Kim, H.Y.; Lee, J.M.; Yokozawa, T.; Sakata, K.; Lee, S. Protective activity of flavonoid and flavonoid glycosides against gluc ose-mediated protein damage. Food Chem. 2010, 126, 892–895.

151. Yu, L.; Chen, C.; Wang, L.-F.; Kuang, X.; Liu, K.; Zhang, H.; Du, J.-R. Neuroprotective effect of kaempferol glycosides against brain injury a nd neuroinflammation by inhibiting the activation of NF-κB and STAT3 i n transient focal stroke. PLoS ONE 2013, 8, e55839.

152. Michael, H.N.; Salib, J.Y.; Eskander, E.F. Bioactivity of Diosmetin Glycosides Isolated from the Epicarp of Date Fruits, Phoenix dactylifera, on the Biochemical Profile of Alloxan Diabetic Male Rats. Phytother. Res. 2012, 27, 699–704.

153. Makino, T.; Kanemaru, M.; Okuyama, S.; Shimizu, R.; Tanaka, H.; Mizukami, H. Anti-allergic effects of enzymatically modified isoquercitrin (α-oligo glucosyl quercetin 3-O-glucoside), quercetin 3-O-glucoside, α-oligoglu cosyl rutin, and quercetin, when administered orally to mice. J. Nat. Med. 2013, 67, 881–886.

154. Xiao, J. Dietary flavonoid aglycones and their glycosides: Which show better bi ological significance? Crit. Rev. Food Sci. Nutr. 2015, 57, 1874–1905.

155. Cao, S.; Ni, B.; Feng, L.; Yin, X.; Dou, H.; Fu, J.; Lin, L.; Ni, J. Simultaneous Determination of Typhaneoside and Isorhamnetin-3-O-Neohesperidoside in Rats After Oral Administration of Pollen Typhae Extract by UPLC-MS/MS. J. Chromatogr. Sci. 2015, 53, 866–871.

156. Zeng, H.; Xue, P.; Su, S.; Huang, X.; Shang, E.; Guo, J.; Qian, D.; Tang, Y.; Duan, J. Comparative Pharmacokinetics of three major bioactive components in rats after oral administration of Typhae Pollen-Trogopterus Feces drug pair before and after compatibility. Daru J. Fac. Pharm. Tehran Univ. Med. Sci. 2016, 24, 2.

157. Lehtonen, H.M.; Lehtinen, O.; Suomela, J.P.; Viitanen, M.; Kallio, H. Flavonol glycosides of sea buckthorn (Hippophae rhamnoides ssp. sinensis) and lingonberry (Vaccinium vitis-idaea) are bioavailable in humans and monoglucuronidated for excretion. J. Agric. Food Chem. 2010, 58, 620–627.

158. Aziz, A.A.; Edwards, C.A.; Lean, M.E.; Crozier, A. Absorption and excretion of conjugated flavonols, including quercetin-4’-O-beta-glucoside and isorhamnetin-4’-O-beta-glucoside by human volunteers after the consumption of onions. Free Radic. Res. 1998, 29, 257–269.

159. Boyle, S.P.; Dobson, V.L.; Duthie, S.J.; Kyle, J.A.; Collins, A.R. Absorption and DNA protective effects of flavonoid glycosides from an onion meal. Eur. J. Nutr. 2000, 39, 213–223.

160. Baell, J.B.; Holloway, G.A. New Substructure Filters for Removal of Pan Assay Interference Compounds (PAINS) from Screening Libraries and for Their Exclusion in Bioassays. J. Med. Chem. 2010, 53, 2719–2740.

161. de Matos, A.M.; Blazquez-Sanchez, M.T.; Sousa, C.; Oliveira, M.C.; de Almeida, R.F.M.; Rauter, A.P. C-Glucosylation as a tool for the prevention of PAINS-induced membrane dipole potential alterations. Sci. Rep. 2021, 11, 4443.