

A comprehensive review of the botany, ethnopharmacology, phytochemistry, and pharmacological activities of two Iranian *Rydingia* species (Lamiaceae)

Aminallah Tahmasebi^{a,b,c,*}, Babak Jamali^a, Vahideh Atabaki^d, Satyajit D. Sarker^e, Lutfun Nahar^{f,*}, Hye Jung Min^{g,*}, Chul Won Lee^{c,*}

^aDepartment of Agriculture, Minab Higher Education Center, University of Hormozgan, Bandar Abbas, Iran

^bPlant Protection Research Group, University of Hormozgan, Bandar Abbas, Iran

^cDepartment of Chemistry, Chonnam National University, Gwangju, Republic of Korea

^dDepartment of Pharmacognosy and Pharmaceutical Biotechnology, Faculty of Pharmacy, Hormozgan University of Medical Sciences, Bandar Abbas, Iran

^eCentre for Natural Products Discovery, School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Byrom Street, Liverpool L3 3AF, UK

^fLaboratory of Growth Regulators, Palacký University and Institute of Experimental Botany, The Czech Academy of Sciences, Šlechtitelů 27, 78371 Olomouc, Czech Republic

^gDepartment of Cosmetic Science, Gwangju Women's University, Gwangju 62396, Republic of Korea

*Correspondence: a.tahmasbi@hormozgan.ac.ir (A.T); nahar@ueb.cas.cz (L.N.); sarock@kwu.ac.kr (H.J.M.); cwlee@jnu.ac.kr (C.W.L.)

Abstract

Rydingia michauxii and *R. persica*, respectively, known as Kase Gol and Goldar in Persian, belong to the family Lamiaceae and they are well known herbal medicine in Iran for the treatment of various diseases, particularly diabetes. This review aims to appraise the phytochemistry, ethnopharmacology, and pharmacological activities of *Rydingia* species growing in Iran and assess their potential in clinical applications. Besides, it critically evaluates existing literature and looks into the perspective for further research and utilization. All available scientific literature was consulted using the database searches involving Google Scholar, PubMed, and Web of Science applying the keyword *Rydingia* and its Syn; *Otostegia*. Only the search results that are associated with the Iranian species *R. michauxii* and *R. persica* are included in this review. α -pinene, carvacrol, caryophyllene oxide, diisooctyl phthalate, dillapiole, eugenol, hexadecanoic acid, and pentacosane are the major constituents of the essential oils of the *Rydingia* species. Additionally,

these species produce bioactive flavonoids, phenolic acids, steroids, and terpenoids. Extracts and active compounds from *Rydingia* species have been reported to possess various pharmacological activities including antidiabetic, anti-inflammatory, antimalarial, antimicrobial, antioxidant, cytotoxic, and lipid-lowering properties. Based on the information available to date on the Iranian *Rydingia* species, it will be worth subjecting these species to further developmental work involving preclinical and clinical trials.

Keywords: Bioactive chemicals; Pharmacology; Phytochemistry; *Rydingia michauxii*; *Rydingia persica*; Traditional Medicine

1. Introduction

The therapeutic use of medicinal plants dates back to thousands of years [1]. Plants produce secondary metabolites with several biological functions [2]. The Lamiaceae is a family of 6900-7200 flowering plants that are distributed within ca. 236 genera [3]. The *Rydingia* (Syn: *Otostegia*) is a Lamiaceae genus comprising only four species *R. integrifolia*, *R. limbata*, *R. michauxii*, and *R. persica*, found in Asia and Northeastern Africa [4, 5].

As an endemic shrub, *R. michauxii* grows in the areas of Fars province in Iran [6, 7]. On the other hand, *R. persica* is found in Afghanistan, Iran, and Pakistan [8-10].

Because of different biological effects offered by *Rydingia* species, they are used in herbal medicine [11-13]. These species possess antidiabetic, anti-inflammatory, antimalarial, antimicrobial, antioxidant, cytotoxic, and lipid-lowering properties. Despite the traditional medicinal uses of *Rydingia* species in Iranian herbal medicine, there is currently no comprehensive review article available on this genus. Therefore, this review, for the first time, critically appraises the phytochemistry and pharmacological properties of two Iranian *Rydingia* species.

2. Materials and Methods

All available scientific literature was obtained using the database searches involving Google Scholar, PubMed, Web of Science, and using the keyword *Rydingia* and its Syn; *Otostegia*. Only the search results that are associated with the Iranian species *R. michauxii* and *R. persica* have been included in this review. The collected data was then categorized into various groups including botany, ethnopharmacology, phytochemistry, and pharmacological activities.

3. Botany

Shrub populations of *R. michauxii* are found near land along or on slopes facing a river (**Fig. 1 A and B**), and morphologically characterized by spines in the leaf axils, spinose, yellow flowers, bracteoles, and few-flowered verticillasters (**Fig. 1 C and D**) [11, 14]. It also contains spines at the upper angle between a leaf stalk and the stem, spiny and durable bracteoles [6]. *R. persica* (Burm.f.) Scheen & V.A. Albert is a spiny shrub reaching approximately 1.5 m in height, featuring rectangular woody stems (**Fig. 1 E and F**). Its leaves are arranged oppositely along the stem, sporting short petioles and obovate-shaped blades, which are densely covered in white hairs. The flowers of this plant exhibit a calyx that resembles a funnel with longitudinal ridges, and they have a white bilabiate corolla with a hairy upper lip [15]. The leaves of this plant are suborbicular-obovate, cuneate in shape, measuring 12 × 12 mm. They possess a prominent covering of glandular hairs and numerous sessile oil globules. The leaf margins are crenate to dentate and feature 0.5-1 mm spines. The petioles can reach up to 10 mm in length. Spines, which can grow up to 20 mm long, are found in the axils of both lower and upper leaves. The verticillasters are comprised of a few flowers and are spaced apart. The bracts are spiny and horizontally spreading, measuring 10 mm in length. The calyx is densely pilose and exhibits clear 10 nerves or ribs. The calyx tube measures 8 mm in length, while the limb spreads to 10 mm in diameter. It is straw-colored, membranous, irregularly lobed, and toothed. The corolla is whitish and reaches a length of 20 mm, with a tube that matches the length of the calyx tube. The upper lip of the corolla is 10 mm long, falcate in shape, and densely villous. The stamens may be included or exerted. The nutlets are obovoid and measure 2-5 mm. They have a rounded apex and often contain only one maturing oil globule [16].



Fig. 1. Distribution of *R. michauxii* in a natural habitat, Kazerun, Fars province (A and B), *R. michauxii* at the vegetative (C) and flowering stages (D) in a natural habitat (Kazerun, Fars province, taken by the author: A.T), *Rydingia persica* at the flowering stage (E and F) from a natural habitat (obtained from the website of the Department of Environment, Fars; <https://idefars.ir/en/content/333#>).

4. Geographical distribution

R. michauxii grows in the limited areas of Fars province, Iran, while *R. persica* is found in Afghanistan, Iran and Pakistan [8-10]. The distribution of *R. persica* in south, south west and south east of Iran includes the arid and subtropical regions in Fars, Kerman, Sistan and Baluchestan, Bushehr, Yazd, and Hormozgan provinces [13, 17] (**Fig. 2**).

Rydingia michauxii (●)

No.	Region	Province
1	Kazerun	Fars
2	Jahrom	Fars

Rydingia persica (●)

No.	Region	Province
1	Jiroft	Kerman
2	Fasa	Fars
3	Bandar Abbas	Hormozgan
4	Neyriz	Fars
5	Hajiabad	Hormozgan
6	Bam	Kerman
7	Saravan	Sistan and Baluchestan
8	Khash	Sistan and Baluchestan
9	Sarbaz	Sistan and Baluchestan
10	Mehrestan	Sistan and Baluchestan
11	Bushehr	Bushehr
12	Dalgan	Sistan and Baluchestan
13	Jam	Bushehr
14	Jahrom	Fars
15	Zabol	Sistan and Baluchestan
16	Firuzabad	Fars
17	Kahnooj	Kerman
18	Bashagard	Hormozgan
19	Iranshahr	Sistan and Baluchestan
20	Darab	Fars
21	Rudan	Hormozgan
22	Herat to Korkhongan	Yazd



Fig. 2. Geographical distribution of *R. michauxii* and *R. persica* in Iran

5. Ethnopharmacology

The aerial parts of *Rydingia* species are used in Iran in the forms of a decoction and an infusion to treat arthritis, blood pressure, bone pain, cardiac distress, constipation, cough, diabetes, fever, gastric discomfort, headaches, itchy throat, menstruation, palpitation, rheumatism, stomachache, and toothache [13, 18-25]. The plant also has analgesic, antianxiety, antidepressant, antidiabetic, antiglycation, antihistaminic, antihyperlipidemic, antihypertensive, anti-inflammatory, antimalarial, antimicrobial, anti-nociceptive, antioxidant, antipyretic, antispasmodic, carminative, healing of burn-wound, hepatoprotective, laxative, morphine withdrawal, mosquito repellent, and sedative properties. There is limited information available on the ethnopharmacology of *R. michauxii*, since the plant species is a rare shrub that grows in limited areas. However, *R. persica* is widely studied in its folk regions with a wide range of pharmacological activities. According to Iranian ancient traditional physician's books and ethnobotanical investigation, *R. michauxii* and *R. persica* have been used for fever/malaria treatment [26, 27]. It has been documented that in the Hormozgan province, leaves, flowers, and thistle of *R. persica* are traditionally utilized as fresh organ decoctions. These are employed as a laxative, to treat coughs, to alleviate cardiac distress, headaches, and gastric discomfort, they offer antipyretic and carminative properties, and, reduce palpitations, regulate blood pressure, and serve as a parasite repellent [19].

The ethnic communities residing in the Kerman province utilize the leaves and flowers of *R. persica* to prepare medicinal decoctions, which are employed to treat liver diseases, alleviate bone and joint pains, combat addiction, lower blood sugar levels, provide relaxation, serve as a tonic for bones and the body, and treatment for chronic and dermatological conditions [28].

Furthermore, among the Baluch tribes in the Saravan region of Iran, the leaves and flowers of *R. persica* are used as decoctions and cataplasms to address various health concerns including the treatment of cardiac distress, diabetes, hypertension, palpitations, rheumatism, constipation and flatulence. Additionally, they are used as antipyretics, to combat colds, gastric discomfort, hyperlipidemia, and as a repellent for parasites. *R. persica* also serves as a sedative, a remedy for headache, and in the management of addiction [29]. This plant is highly regarded in the folk medicine of Jam and Riz (Bushehr province) in the treatment of bone pain, burn, constipation, diabetes, eye swelling, fever, headache, and parasite infections [30], while used in Darab (Fars province) as an anti-inflammatory, antimicrobial, and antioxidant agent [31]. In addition to their

medicinal uses, flowers of this plant are widely incorporated as additives to butter, meat, milk and yoghurt, illustrating its culinary and flavor-enhancing applications within the region [32].

6. Phytochemistry

The following section explores the analysis of the phytochemical composition found within the essential oils and non-volatile compounds extracted from *R. michauxii* and *R. persica*.

Essential oil of *R. michauxii* is characterized by a complex profile of chemical components. The composition of the essential oil varies significantly across different growth stages, with different phytochemical profiles observed during the dormant, vegetative, and flowering stages. Major compounds such as eugenol, carvacrol, and caryophyllene oxide dominate specific growth stages, suggesting the dynamic nature of the plant's chemical composition. Additionally, non-volatile compounds in *R. michauxii*, including polyphenols, iridoids, labdane diterpenes, and phenylethanoid glycosides, contribute to the plant's chemical complexity.

Notable differences in chemical composition emerge between flower and leaf samples of *R. persica*. Here, monoterpenes and sesquiterpenes play pivotal roles in shaping the oil's profile. Moreover, the plant's non-volatile compounds—flavonoids, diterpenoids, and polyphenolics—further enrich its chemical diversity.

6.1. Composition of *Rydingia michauxii* essential oil

A total of forty-five chemical components, dillapiole (23.9%), 2-methylbenzofuran (12.9%), and α -pinene (8.1%) being the major ones, were found in the essential oil of *R. michauxii* [7]. Two phenylpropanoids, dillapiole and 2-methylbenzofuran, were the dominant constituents, accounting for 36.8% of the total essential oil [7].

R. michauxii essential oil contained eighty compounds including caryophyllene oxide (20.1%), *trans*-verbenol (10.2%), linalool (5%), and humulene epoxide II (4.6%) [11]. The essential oil composition of *R. michauxii* during various growth stages, i.e., dormant, vegetative, and flowering phases, was also reported, where it was observed that the different growth stages were associated with the distinct phytochemical profiles of the essential oils [33]. Specifically, the essential oil consisted of fifty-four, sixty-five, and fifty-nine components in the respective growth stages. The major chemical compounds of *R. michauxii* during the dormancy stage were found to be eugenol (36.81%), eugenol acetate (21.02%) and carvacrol (9.35%).

At the vegetative growth stage, carvacrol (16.08%), eugenol (13.23%), cuminaldehyde (9.63%), and linalool (8.28%) were the major ones. The main volatile components at the flowering stage were carvacrol (14.2%), eugenol (8.98%), δ -cadinene (8.9%), caryophyllene oxide (8.43%), and *n*-hexadecanoic acid (7.07%). The highest levels of eugenol (36.81%), eugenol acetate (21.02%), (*trans*)-caryophyllene (2.52%), and bornyl acetate (1.58%) were detected during the plant dormancy phase. During the vegetative growth, the highest concentrations were found for carvacrol (16.08%), cuminaldehyde (9.63%), linalool (8.28%), *epi*- α -cadinol (4.33%), *trans*- α -bergamotene (2.88%), thymol (1.63%), methyl eugenol (1.4%), and thujadiene (1.37%). The highest concentrations of δ -cadinene (8.9%), caryophyllene oxide (8.43%), (*cis*)-4-decen-1-ol (3.02%), (*cis*)-4-decen-1-ol (3.02%), and γ -cadinene (2.54%) were found during the flowering stage [33]. The structure of major compounds found in *R. michauxii* essential oils is shown in **Fig. 3**. The chemical composition of *R. michauxii* essential oil exhibited significant variation based on geographical locations and developmental stages (**Table 1**).

Table 1. Chemical composition of the major constituents of the essential oils of *Rydingia michauxii* at different geographical locations and developmental stages

Dominant constituents of the essential oils	Developmental stage	Location	Reference
α -pinene	Flowering	Chahzangooleh, Fars province	[7]
Carvacrol	Dormant	Kazerun, Fars province	[33]
Carvacrol	Flowering	Kazerun, Fars province	[33]
Carvacrol	Vegetative	Kazerun, Fars province	[33]
Caryophyllene oxide	Flowering	Kazerun, Fars province	[33]
Caryophyllene oxide	Flowering	Kazerun, Fars province	[11]
Cuminaldehyde	Vegetative	Kazerun, Fars	[33]

		province	
Dillapiol	Flowering	Chahzangooleh, Fars province	[7]
δ -cadinene	Flowering	Kazerun, Fars province	[33]
Eugenol	Flowering	Kazerun, Fars province	[33]
Eugenol	Vegetative	Kazerun, Fars province	[33]
Eugenol	Dormant	Kazerun, Fars province	[33]
Eugenol acetate	Dormant	Kazerun, Fars province	[33]
<i>n</i> -Hexadecanoic acid	Flowering	Kazerun, Fars province	[33]
Humulene epoxide II	Flowering	Kazerun, Fars province	[11]
Linalool	Flowering	Kazerun, Fars province	[11]
Linalool	Vegetative	Kazerun, Fars province	[33]
2-Methylbenzofuran	Flowering	Chahzangooleh, Fars province	[7]
<i>Trans</i> -verbenol	Flowering	Kazerun, Fars province	[11]

185
186

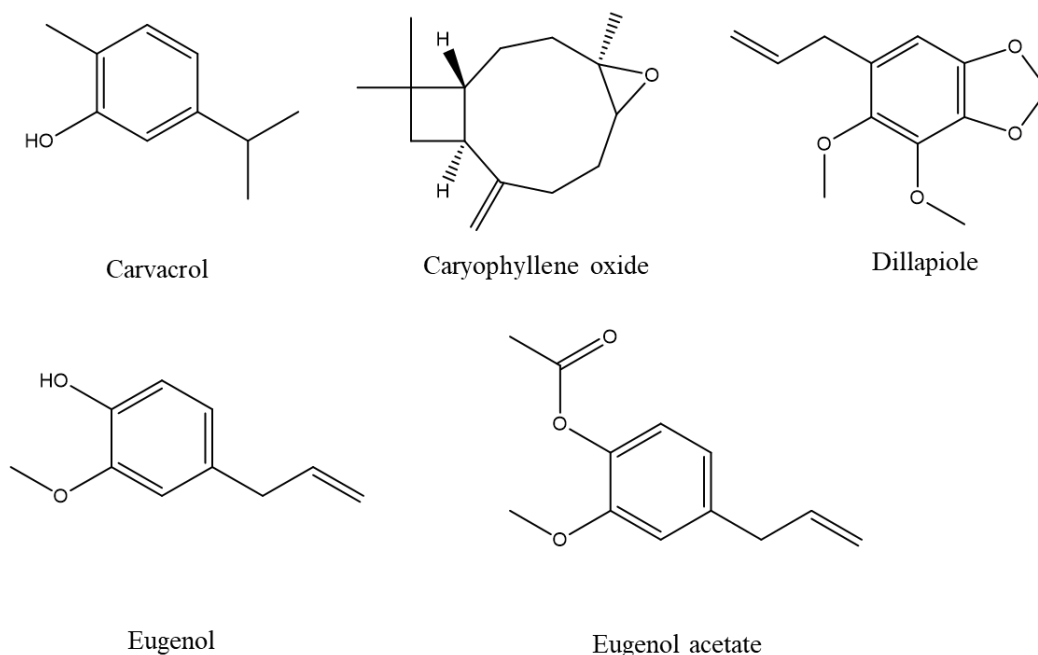


Fig. 3. The chemical structures of carvacrol, caryophyllene oxide, dillapiolene, eugenol, and eugenol acetate

6.2. Components of *Rydingia persica* essential oil

Seventeen compounds were identified in the essential oil extracted from the flowering aerial parts of samples collected from the Kerman province, accounting for 92.06% of the oil composition [34]. This essential oil was abundant in non-terpenes (70.93%). Specifically, it contained sesquiterpenes at a concentration of 15.4% and monoterpenes at 5.73%. The major compounds were hexadecanoic acid (31.73%), pentacosane (29.51%), α -copaene-8-ol (5.93%), and hexadecanoic acid methyl ester (4.76%)

The oil samples extracted from both the flowers and leaves of *R. persica* in the Sistan and Baluchestan regions revealed the presence of different compounds. In the flower oil sample, a total of 33 compounds were identified, constituting 90.29% of the oil. In the leaf oil sample, 26 compounds were detected, accounting for 83.27% of the oil. The essential oil from the flower samples collected from Sistan and Baluchestan exhibited a composition characterized by monoterpenes (52.82%), sesquiterpenes (18.23%), and non-terpenes (10.20%). The essential oil from the leaves contained monoterpenes (44.6%), sesquiterpenes (19.24%), and non-terpenes (15.23%) [34].

In the flower oil sample, α -pinene (13.62%), verbenol (9.22%), linalool (6.76%), hexadecane

(5.52%), caryophyllene oxide (4.84%), pentadecane (4.56%), and *trans*-carveol (4.00%) were the major components. In the leaf oil sample, the dominant components included hexahydrofarnesyl acetone (14.34%), verbenol (10.16%), geranyl acetone (6.47%), pentadecane (5.94%), hexadecane (5.86%), α -pinene (4.48%), and *trans*-anethole (4.47%) [34].

A total of forty-four components, constituting 89.3% of the entire essential oil composition extracted from the aerial parts of *R. persica*, were identified. The primary constituents of this oil were dillapiole (43.1%), *trans*-verbenol (9.6%) and hexadecanoic acid (5.7%) [35]. Caryophyllene oxide, β -sinesal, and β -caryophyllene were identified as significant constituents of this species [13]. The essential oils from the aerial parts of *O. persica* at two different stages, flowering and fruiting, yielded distinctly different chemical compositions. In the flowering stage oil, twenty-eight components were identified, representing 97.59% of the oil composition. The primary compounds in this oil were α -pinene (17.21%), 1-octen-3-ol (13.44%), and cubenol (7.27%). In the fruiting stage oil, thirty-one components were identified, constituting 94.61% of the oil composition. The dominant constituents in this oil were di-isooctyl phthalate (45%) and hexadecanoic acid (11.07%) [36].

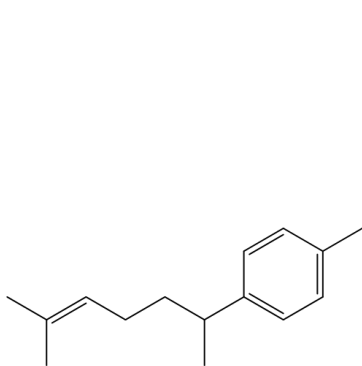
The chemical composition of the essential oil extracted from *R. persica* was analyzed using gas chromatography-mass spectrometry (GC-MS), revealing different compositions in the leaf and flower parts of the plant. In the leaves, twelve compounds were identified, with the highest essential oil components being thymol (12.0%), β -turmerone (8.0%), carvacrol (7.0%), and methyl ionone (6.3%). In flowers, thirty-one compounds were identified, and the major constituents included benzene, 1-(1,5-dimethyl-4-hexenyl)-4-methyl- (13.0%), *p*-mentha-1,5,8-triene (8.9%), methyl Ionone (6.8%), and spathulenol (5.9%) [37]. **Fig. 4** illustrates the chemical structures of several key components found in the essential oils of *R. persica*. Also, the chemical composition of the main compounds in *R. persica* essential oil was shown in **Table 2**.

Table 2. Variations in the chemical composition of key constituents in *Rydingia persica* essential oil across different geographical locations and developmental stages, or plant parts.

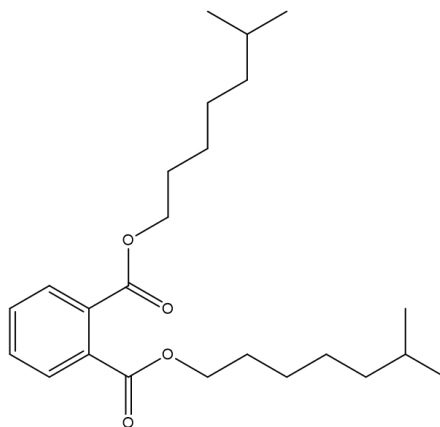
Dominant constituents of the essential oils	Developmental stage/plant part	Location	Reference
α -pinene	Flower	Sistan and Baluchestan	[34]
α -pinene	Flowering	Dehbakri	[36]
Benzene, 1-(1,5-dimethyl-4-hexenyl)-	Flower	Mehrestan	[37]

4-methyl- (CAS)			
β -turmerone	Leaf	Mehrestan	[37]
Carvacrol	Leaf	Mehrestan	[37]
Cubenol	Flowering	Dehbakri	[36]
Diisooctyl phthalate	Fruiting	Dehbakri	[36]
Dillapiole	Flowering	Neyriz	[35]
Geranyl acetone	Leaf	Sistan and Baluchestan	[34]
Hexadecanoic acid	Flowering	Neyriz	[35]
Hexadecanoic acid	Fruiting	Dehbakri	[36]
Hexadecanoic acid	Flowering	Kerman	[34]
Hexahydrofarnesyl acetone	Leaf	Sistan and Baluchestan	[34]
Linalool	Flower	Sistan and Baluchestan	[34]
Methyl ionone	Leaf	Mehrestan	[37]
Methyl ionone	Flower	Mehrestan	[37]
1-Octen,3-ol	Flowering	Dehbakri	[36]
<i>p</i> -mentha-1,5,8-triene	Flower	Mehrestan	[37]
Pentacosane	Flowering	Kerman	[34]
Spathulenol	Flower	Mehrestan	[37]
Thymol	Leaf	Mehrestan	[37]
<i>Trans</i> -verbenol	Flowering	Neyriz	[35]
Verbenol	Flower	Sistan and Baluchestan	[34]
Verbenol	Leaf	Sistan and Baluchestan	[34]

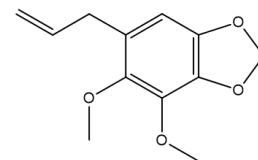
234
235
236



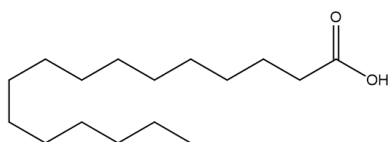
Benzene, 1-(1,5-dimethyl-4-hexenyl)-4-methyl-



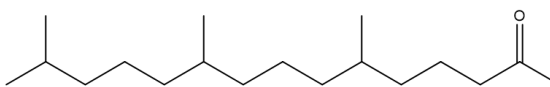
Di-isooctyl phthalate



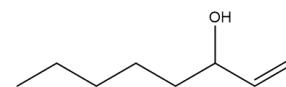
Dillapiole



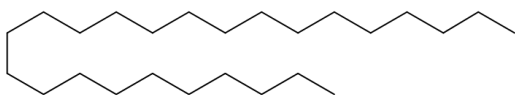
Hexadecanoic acid



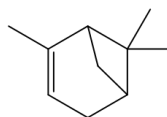
Hexahydrofarnesyl acetone



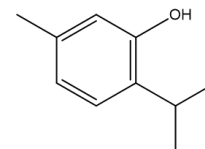
1-Octen-3-ol



Pentacosane



α-Pinene



Thymol

Fig. 4. Chemical structures of some major constituents in the essential oil of *Rydingia persica*; α-pinene, benzene, 1-(1,5-dimethyl-4-hexenyl)-4-methyl-, di-isooctyl phthalate, dillapiole, hexadecanoic acid, hexahydrofarnesyl acetone, 1-octen-3-ol, pentacosane, and thymol

6.3. Non-volatile compounds of *Rydingia michauxii*

Extracts of *R. michauxii* were examined during three growth stages to characterize its constituents [14]. Many polyphenols were found, e.g., *O*- and *C*-glycosylated flavonoids, and iridoids, and phenylethanoid glycosides. Labdane diterpenes were the dominant compounds during the vegetative and flowering stages, making up 20% of the total extract. The phytochemicals identified in the extracts contained chemically heterogeneous compounds, including antirrhinoside, iridoid, labdane derivatives, lignan medioresinol, and other phenolics. The findings indicated the presence of flavonol glycosides, both *C*- and *O*-derivatives, and other phenols, particularly derivatives of caffeic acid. The extracts of the three stages yielded several polyphenols, including *C*-glycosylated

flavonoids, gallic acid derivatives, hydroxycinnamic, O-glycosylated flavonoids, and phenylethanoid derivatives. Only during the vegetative and flowering stages, terpene derivatives could be detected. Several phenylethanoid glycosides were found in the extracts, including, echinacoside, isoverbacoside, derivatives, and verbascoside as well as several well-known flavonoids like apigenin, kaempferol, luteolin and their glycosides. However, O-glycosylated and C-glycosylated flavonoids, apigenin and luteolin derivatives could not be detected during the dormant stage. More phytochemicals were present during the vegetative and flowering stages compared with the dormant plants. Among the extracts, the flowering extract contained the highest levels of flavonoids and labdane derivatives [14]. The chemical structures of the major non-volatile compounds of *R. michauxii* are shown in **Fig. 5**.

The LC-MS analysis detected several compounds in *R. michauxii* methanolic extract [14]. Some of these compounds have been extensively reviewed, for example, apigenin [38], chlorogenic acid [39], echinacoside [40, 41], hydroxycinnamic acid [42], kaempferol [43], luteolin [44, 45], and verbascoside [46, 47].

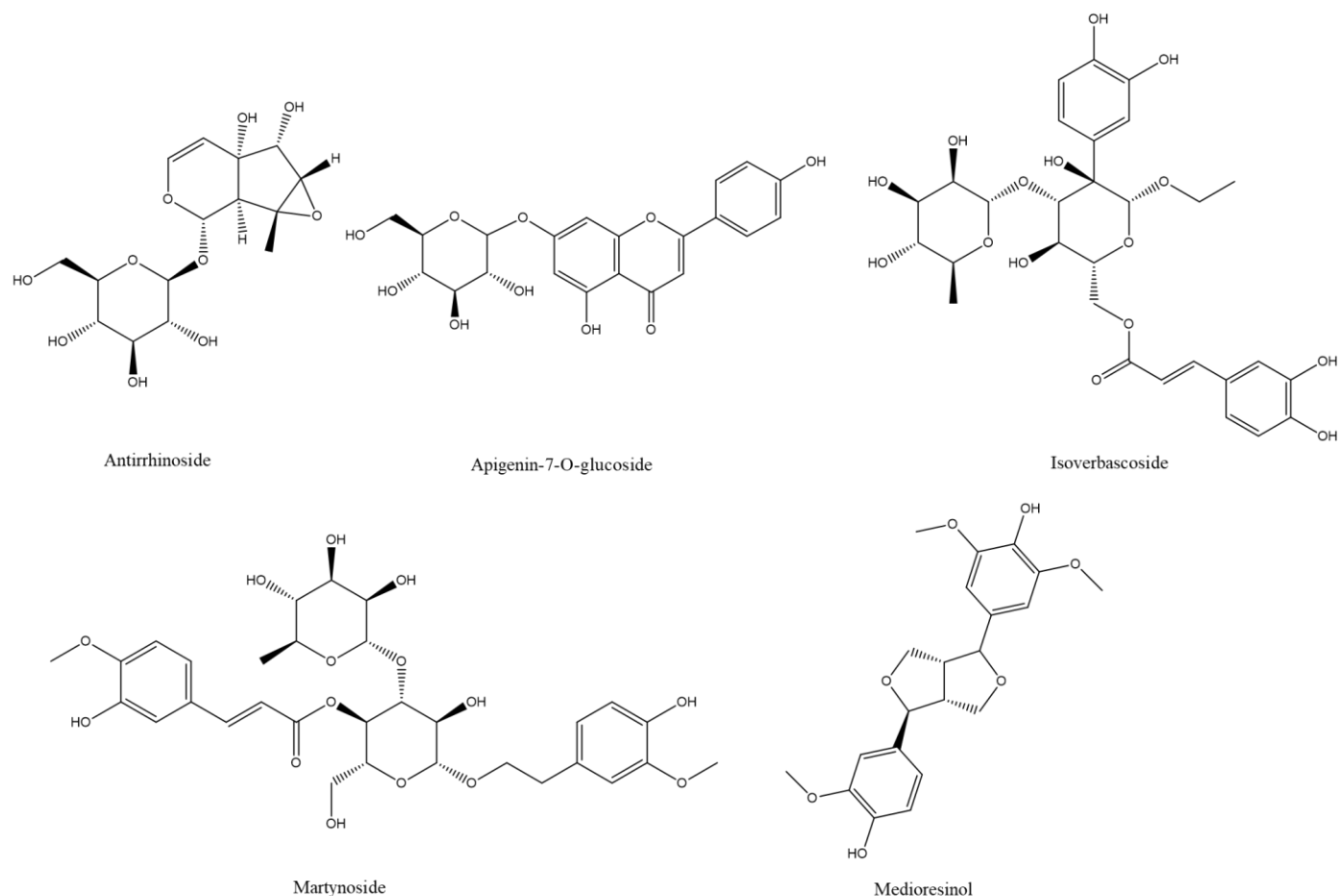


Fig. 5. The chemical structures of some constituents of the extracts of *Rydingia michauxii*; antirrhinoside, apigenin 7-O-glucoside, isoverbascoside, martynoside, and medioresinol

6.4. Non-volatile compounds of *Rydingia persica*

Eleven compounds specifically β -amyrin, caffeic acid, campesterol, ceryl alcohol, eugenol, geraniol, hentriacontane, *p*-hydroxybenzoic acid, β -sitosterol, β -sitosteryl acetate, and stigmasterol were extracted from the aerial parts of *R. persica* [48]. For the first time, four recognized diterpenoids from the clerodane and tetracyclic diterpene categories were discovered in the blooming aerial segments of *R. persica*. The dichloromethane extract of the aerial parts of *R. persica* was found to contain a high amount of terpenoids [49].

The extracts from the aerial parts of *R. persica* were found to contain four flavonoids isovitexin, kaempferol, morin, and quercetin [50]. From the ethyl acetate-soluble fraction of the ethanol extract obtained from the aerial parts of this plant, four labdane diterpenoids, 15,16-epoxy-

3 α ,7 β ,9 α -trihydroxylabdan-13(16),14-dien-6-one, 15,16-epoxy-3 α ,7 α ,9 α -trihydroxylabdan-13(16),14-dien-6-one, and 9,13,15,16-diepoxy-3 α ,7 β ,15 α (β)-trihydroxy-labdan-6-one were isolated [51]. Phytochemical analyses of the ethyl acetate extract obtained from the aerial parts of *R. persica* revealed the presence of two furano-diterpenes (15,16-epoxy-3 α ,7 β ,9 α -trihydroxylabdan-13-(16),14-dien-6-one and 15,16-epoxy-3 α ,7 α ,9 α -trihydroxylabdan-13-(16),14-dien-6-one) and two spiro labdane-type diterpenes (9,13,15,16-diepoxy-3 α ,7 β ,15 α (β)-trihydroxy-labdan-6-one). Among these compounds, the two spiro diterpenes are novel and reported for the first time, while the two furano-diterpenes are newly reported in this plant. All four compounds belong to the labdane class of diterpenes [51].

The extracts from *R. persica* were found to contain many polyphenolic compounds, with caffeic acid, sinapic acid, and *trans*-ferulic acid being the predominant compounds among them. Additionally, gallic acid, *p*-coumaric acid, and vanillin were also identified as polyphenols in the extract, although in lower quantities [52].

Previous studies revealed that the methanolic extract of *R. persica* is a rich source of flavonoids, including apigenin derivatives, kaempferol, quercetin, and 3',7-dihydroxy-4',6,8-trimethoxy-flavone [24, 50, 53]. Other flavonoids, including vicenin-2 (apigenin 6,8-di-C- β -D-glucoside) and isorhamnetin-3-*O*-glucoside were identified in the methanolic extract of *R. persica* [21]. Phytochemical analysis of the plant extract using GC-MS identified thymol as the predominant phytoconstituent in the extract [54]. The phytochemical screening of the *R. persica* crude extract revealed the presence of flavonoids, phenolic acids, and steroids/triterpenoids. Specifically, chrysoeriol was isolated from the ethyl acetate fraction, while three apigenin derivatives, namely apigenin 7-*O*-glucoside, echinaticin, and 6-methylapigenin, were isolated from and identified in the methanol fraction [53]. The chemical structures of some major constituents of the extracts of *R. persica* are presented in **Fig. 6**.

In summary, these phytochemical analyses have revealed the chemical diversity present in the essential oils and non-volatile extracts of *R. michauxii* and *R. persica*. The essential oil compositions of both species exhibited significant variation across different growth stages, geographical locations, and plant parts, indicative of their plasticity in biosynthesizing an array of volatile terpenes and phenylpropanoid derivatives. The non-volatile fractions were particularly enriched in polyphenolic compounds, including flavonoids, phenolic acids, iridoids, and labdane-type diterpenes. Several diterpenes were isolated from *R. persica* for the first time. The

identification of these chemically heterogeneous phytoconstituents provides valuable insights into the biochemical pathways operating in these species and their evolutionary adaptation to environmental cues. Collectively, these findings contribute significantly to our understanding of the phytochemical diversity within the *Rydingia* genus and underscore the importance of exploring underutilized plant resources for bioactive metabolites.

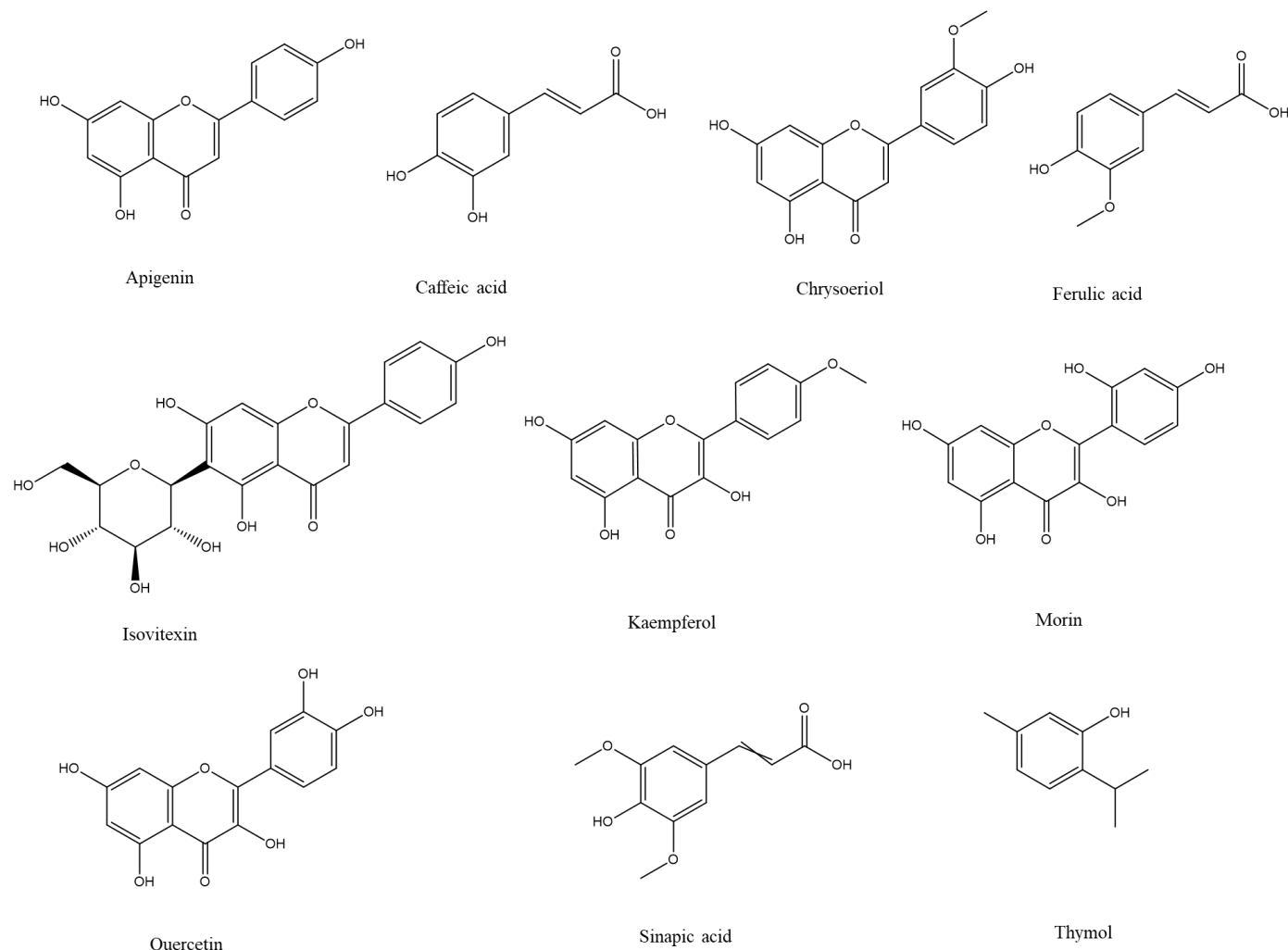


Fig. 6. The chemical structures of some constituents of the extracts of *Rydingia persica*; apigenin, caffeic acid, chrysoeriol, ferulic acid, isovitexin, kaempferol, morin, quercetin, sinapic acid, and thymol

7. Pharmacological activities

The genus *Rydingia* has been demonstrated to possess various pharmacological activities including antidiabetic, anti-inflammatory, antimalarial, antimicrobial, antioxidant, cytotoxic, and lipid-lowering properties. The pharmacological activities of *R. michauxii* and *R. persica* are summarized in **Fig. 7** and **Table 3**.



Fig. 7. A summary of pharmacological properties of *Rydingia michauxii* and *R. persica*

346 **Table 3.** Summary of the pharmacological activities of *Rydingia michauxii* and *Rydingia persica*
347

Plant species	Pharmacological activities	Extract/essential oil	Study design	Model/test	Active Dosage	References
<i>R. persica</i>	Anti-atherosclerosis	Hydroalcoholic extract	<i>In-vivo</i>	Wistar rats	25 mg/kg	[55]
<i>R. persica</i>	Anticonvulsant activity	Methanolic extract	<i>In-vivo</i>	Albino mice	800 mg/kg	[56]
<i>R. persica</i>	Antidiabetic activity	Aqueous extract	<i>In-vivo</i>	Wistar rats	400 mg/kg	[57]
<i>R. persica</i>	Antidiabetic activity	Aqueous extract	<i>In-vivo</i>	Wistar rats	200-400 mg/kg	[58]
<i>R. persica</i>	Antidiabetic activity	Ethanollic extract	<i>In-vivo</i>	Sprague–Dawley rats	500 mg/kg	[59]
<i>R. persica</i>	Antidiabetic activity	Ethanollic extract	<i>In-vivo</i>	Wistar rats	300 mg/kg	[60]
<i>R. persica</i>	Antidiabetic activity	Ethanollic extract	<i>In-vivo</i>	Sprague–Dawley rats	500 mg/kg	[61]
<i>R. persica</i>	Antidiabetic activity	Methanolic extract	<i>In-vivo</i>	Wistar rats	300 mg/kg	[62]
<i>R. persica</i>	Antidiabetic activity	Methanolic extract	<i>In-vivo</i>	Wistar rats	300 mg/kg	[63]
<i>R. persica</i>	Antidiabetic activity	Methanolic extract	<i>In-vivo</i>	Wistar rats	300 mg/kg	[54]
<i>R. persica</i>	Antidiabetic activity	Methanolic extract	<i>In-vivo</i>	Wistar rats	300 mg/kg	[64]
<i>R. persica</i>	Antidiabetic activity	Methanolic extract	<i>In-vivo</i>	Wistar rats	100-300 mg/kg	[65]
<i>R. persica</i>	Antidiabetic activity	Methanolic extract	<i>In-vivo</i>	NMRI mice	400 mg/kg	[53]
<i>R. persica</i>	Antidiabetic activity	Powder	<i>In-vivo</i>	Wistar rats	200, 400, and 600 mg/kg	[66]
<i>R. persica</i>	Antihypertensive activity	Ethanollic extract	<i>In-vivo</i>	Wistar rats	400 mg/kg	[23]
<i>R. persica</i>	Anti-inflammatory activity	Ethanollic extract	<i>In-vitro</i>	The human red blood cell membrane stabilization assay	50-300 µg/mL	[67]
<i>R. persica</i>	Anti-inflammatory activity	Methanolic extract	<i>In-vivo</i>	Albino Wistar rats	100 mg/Kg	[21]
<i>R. persica</i>	Anti-ischemia/reperfusion injury	Ethanollic extract	<i>In-vivo</i>	Wistar rats	300 mg/kg	[68]
<i>R. persica</i>	Antimalarial activity	Ethanollic extract	<i>In-vivo</i>	Sourian mice	450 mg/kg	[69]
<i>R. persica</i>	Antimalarial	Ethanollic	<i>In-vivo</i>	Sourian	450	[70]

	activity	extract		mice/fixed ratio method	mg/kg	
<i>R. persica</i>	Antimicrobial activity	Ethanolic extract	<i>In- vitro</i>	Agar disk diffusion assay MIC	300 µg/ mL	[67]
<i>R. persica</i>	Antimicrobial activity	Ethanolic extract	<i>In- vitro</i>	MFC	75-150 µg/mL	[67]
<i>R. persica</i>	Antimicrobial activity	Methanolic, chloroform, and hexane extracts	<i>In- vitro</i>	MIC	75-300 µg/mL	[71]
<i>R. persica</i>	Antimicrobial activity	Methanolic extract	<i>In- vitro</i>	MIC Disk diffusion method	0.62-20 mg/mL	[72]
<i>R. persica</i>	Antinociceptive activity	Methanolic extract	<i>In-vivo</i>	Albino Wistar rats	0.5-2 mg/cc	[21]
<i>R. persica</i>	Antioxidant activity	Essential oil	<i>In- vitro</i>	DPPH	100 and 200 mg/disk	[36]
<i>R. persica</i>	Antioxidant activity	Essential oil	<i>In- vitro</i>	DPPH	19.8 µg/mL	[34]
<i>R. persica</i>	Antioxidant activity	Ethanolic extract	<i>In- vitro</i>	DPPH ABTS	9.76 µg/mL	[67]
<i>R. michauxii</i>	Antioxidant activity	Methanolic extract	<i>In- vitro</i>	DPPH FRAP	300 µg/mL	[73]
<i>R. persica</i>	Antioxidant activity	Methanolic and ethyl acetate extracts	<i>In- vitro</i>	DPPH	465.4 µg DW/mL	[74]
<i>R. persica</i>	Antioxidant activity	Methanolic extract	<i>In- vitro</i>	DPPH	26.7 µM/g DW	[53]
<i>R. persica</i>	Anti-sclerotic effect	Ethanolic extract	<i>In-vivo</i>	Wistar rats	nd	[75]
<i>R. persica</i>	Bone protective effects	Ethanolic extract	<i>In-vivo</i>	Wistar rats	0.49 mg/mL	[76]
<i>R. persica</i>	Bone protective effects	Ethanolic extract	<i>In-vivo</i>	Wistar rats	300 mg/kg	[60]
<i>R. persica</i>	Burn wound healing	Methanolic extract	<i>In-vivo</i>	Wistar rats	200 mg/kg	[22]
<i>R. michauxii</i>	Cytotoxic activity	Dichloromethane extract	<i>In- vitro</i>	Oral squamous	9 g dried extract in 8 ml of distilled water and 92 mg Eucerin	[77]

				cell carcinoma cell line/ MTT assay	mg/mL	
<i>R. michauxii</i>	Cytotoxic activity	Methanolic extract	<i>In-vitro</i>	MCF-7 human breast cancer cell line/ MTT assay	1.23-3.2 mg/mL	[78]
<i>R. persica</i>	Cytotoxic activity	Ethanollic extract	<i>In-vitro</i>	human umbilical vein endothelial cells/ MTT assay	500 to 1000 µg/mL	[79]
<i>R. michauxii</i>	Cytotoxic activity	Methanolic extract	<i>In-vitro</i>	WEHI-164, MCF-7, MDBK, A-549, and HepG-2 cell lines/ MTT assay	>50 µg/mL	[80]
<i>R. persica</i>	Hepatoprotective activity	Ethanollic extract	<i>In-vivo</i>	Wistar rats	80 and 120 mg/kg	[20]
<i>R. persica</i>	Hepatoprotective activity	Methanolic extract	<i>In-vivo</i>	Wistar rats	300 mg/kg	[81]
<i>R. michauxii</i>	Lipid lowering activity	Methanolic extract	<i>In-vitro</i>	Human hepatocarcinoma cell line Huh7	50 µM	[14]
<i>R. persica</i>	Reduction in morphine withdrawal symptoms	Ethanollic extract Hexane extract	<i>In-vivo</i>	Albino mice	1500 mg/kg	
					500, 1000 and 1500 mg/kg	[82]
<i>R. persica</i>	Renoprotective activity	Ethanollic extract	<i>In-vivo</i>	Wistar rats	500 mg/kg	[83]

7.1. Antimicrobial activity

In the study led by Asghari et al. [71], the antimicrobial activities of the methanolic, chloroform, and *n*-hexane extracts of *R. persica* were assessed using the well plate method, Minimum

Inhibitory Concentration (MIC) determination, and Minimum Bactericidal Concentration (MBC) determination methods. The antimicrobial activity of *R. persica* extracts was observed against Gram-positive strains, including *Enterococcus faecalis*, *Listeria monocytogenes*, *Staphylococcus epidermidis*, and *S. aureus*. The MIC values for these extracts ranged between 0.62 mg/mL and 20 mg/mL. Specifically, the methanolic extract exhibited antimicrobial activity within the concentration range of 3.12 mg/mL to 100 mg/mL. The chloroform extract demonstrated antimicrobial activity within the range of 2.5 mg/mL to 40 mg/mL. Meanwhile, the *n*-hexane extract showed antimicrobial activity against *S. aureus*, *S. epidermidis*, and *E. faecalis* within the range of 5 mg/mL to 80 mg/mL. The MBC values, which represent the concentration required to kill the microorganisms, were found to be two, four, or eight times higher than the MIC values for the corresponding extracts. This suggests that while the extracts inhibit the growth of these Gram-positive strains at lower concentrations (MIC), higher concentrations (MBC) are needed to achieve bactericidal effects [71]. In the antibacterial assessment of the *R. persica* leaf extract at a concentration of 300 µg/mL using the agar disk diffusion assay [67], the extract exhibited the highest inhibition zone of 22 mm against *S. aureus* and the lowest inhibition zone of 15 mm against *E. coli*. Regarding the MIC values determined for the *R. persica* leaf extract, they ranged from 75 µg/mL to 150 µg/mL. The MBC values assessed for the *R. persica* leaf extract ranged from 150 µg/mL to 300 µg/mL. Furthermore, for antifungal activity, the minimum fungicidal concentration values of the *R. persica* leaf extract were found to be in the range of 75 µg/mL to 300 µg/mL, indicating its effectiveness against fungal organisms within this concentration range [67]. The aerial parts of the methanol extract of *R. persica* exhibited the most significant antimicrobial effect, with the largest inhibition zones measuring 15 and 11.7 mm against *E. coli* and *B. subtilis*, respectively. In addition, the MIC values of the extract varied from 0.5 mg/cc to 2 mg/cc against several bacterial strains [72].

7.2. Antimalarial activity

The antiplasmodial activity of *R. michauxii* extract was previously documented [26, 27]. In this regard, *R. michauxii* showed 25 % heme detoxification inhibition [27].

The emergence of chloroquine-resistant strains of *Plasmodium falciparum* in many malaria-prone areas has created challenges for treating acute cases of the disease, especially when using monotherapy regimens [70]. The effectiveness of combining chloroquine (CQ) with *R. persica* (RP) was investigated against both chloroquine-sensitive and chloroquine-resistant strains of *P.*

berghei in Sourian mice using an *in vivo* adapted fixed ratios method. Their findings indicated that certain combinations, such as "30% CQ + 70% RP," "50% CQ + 50% RP," and "70% CQ + 30% RP," were more effective than other combinations when assessed against the chloroquine-sensitive strain of malaria. Their results suggest that combining chloroquine and *R. persica* may offer a promising approach to enhance the effectiveness of malaria treatment, particularly in areas where chloroquine resistance is prevalent. The fixed ratio combinations of *R. persica* and chloroquine displayed an additive effect when evaluated against the chloroquine-resistant strain of malaria. Importantly, the study found no evidence of toxicity associated with these combinations in mice. *R. persica* was found to enhance the effectiveness of chloroquine against the chloroquine-sensitive strain of *P. berghei*, but this potentiation effect was not observed in the case of the chloroquine-resistant strain of the parasite. The study also suggests that the specific combination of 70% *R. persica* and 30% chloroquine was particularly effective, indicating that even a lower amount of chloroquine could enhance the effect of *R. persica* against the chloroquine-sensitive strain. The results further implied that chloroquine and *R. persica* may share similar mechanisms of action against the parasite, but the development of resistance to chloroquine in *P. berghei* interferes with the effective interaction between the plant extract and chloroquine [70]. Additionally, *R. persica* was found to have a modest effect against the sexual forms of the chloroquine-sensitive *P. berghei* strain. This suggests that *R. persica* may have potential utility in targeting different stages of the malaria parasite's life cycle [69].

7.3. Antioxidant activity

Methanolic extracts of *R. michauxii* showed ferric reducing antioxidant activity of 26.7 ± 1.3 μ M/g DW and an IC₅₀ 2,2-diphenyl-1-picrylhydrazyl (DPPH) scavenging activity of 465.4 ± 76.6 μ g DW/mL [73].

In a recent study done by Tofighi et al. [34], the antioxidant activities of the essential oils extracted from *R. persica* were evaluated using a free radical scavenging method with DPPH. The results showed that the IC₅₀ (the concentration at which 50% of the free radicals are scavenged) of the essential oil of samples collated from Sistan and Baluchestan was more potent, with a value of 9.76%, than the positive control vitamin E (with an IC₅₀ of 12.02%) and butylated hydroxyanisole (BHA) (with an IC₅₀ of 24.16%) [34].

In another study led by Tofighi et al. [74], the methanol and ethyl acetate fractions obtained from the aerial parts of the plant during the flowering stage exhibited significant antioxidant activities.

The methanol fraction displayed potent activity with an inhibition rate of 91.53% against free radicals. Likewise, the ethyl acetate fraction demonstrated a moderate antioxidant activity with an inhibition rate of 82%. Notably, the methanol fraction showed comparable antioxidant activity to vitamin E, with an inhibition rate of 94.69%, and was also on par with the positive control butylated hydroxytoluene (BHT) which had an inhibition rate of 90.6% [74].

Similarly, in the study conducted by Sharififar et al. [36], the essential oil extracted from *R. persica* during the flowering stage demonstrated strong antioxidant and free radical scavenging activity, as indicated by its IC₅₀ value of 19.8 ± 1.8 µg/mL. This activity was similar to that of BHA and ascorbic acid, which had IC₅₀ values of 15.2 ± 1.1 and 17.4 ± 1.3 µg/mL, respectively. Furthermore, when evaluated in the ammonium thiocyanate system to assess its ability to inhibit the oxidation of linoleic acid, the essential oil from the flowering stage of *R. persica* exhibited a significant inhibition rate of $93.5 \pm 2.8\%$. The higher antioxidant activity observed in the essential oil from the flowering stage compared to the fruiting stage may be attributed to its higher content of monoterpenes, especially oxygenated species. These results highlighted the potential of *R. persica* essential oil, particularly from the flowering stage, as a natural antioxidant with properties similar to or even higher than known antioxidants like BHA [36].

Additionally, the antioxidant potential of various extracts derived from the aerial parts of *R. persica* was assessed using β-carotene bleaching and lipid peroxidation models [50]. Among the extracts, the methanolic extract of the plant demonstrated the highest antioxidant activity. Through column and paper chromatography, five compounds were isolated and purified from the methanolic extract. Notably, three of these isolated flavonols exhibited antioxidant activity, on par with BHA and vitamin E, in both experimental models. These active compounds were identified as morin, kaempferol, and quercetin. Additionally, isovitexin, also displayed antioxidant properties, albeit weaker in comparison to the flavonols. Four of these compounds, specifically isovitexin, kaempferol, morin, and quercetin, displayed antioxidant activity, as confirmed by their spectral data [50]. Similarly, the methanolic extract demonstrated antioxidant properties, effectively inhibiting the peroxidation of linoleic acid. Within this methanolic extract, two antioxidant compounds, morin and quercetin, were isolated through column and paper chromatography. These two compounds exhibited substantial antioxidant activity, on par with that of BHA and α-tocopherol [84].

In fish fed with diets containing *R. persica* powder (1% and 1.5%), the levels of catalase,

glutathione peroxidase, and superoxide dismutase were found to be the highest. Additionally, as the amount of plant powder in the diet increased, there was a significant reduction in the levels of malondialdehyde. *R. persica* powder could exert a beneficial influence on serum antioxidant parameters in the tested fish [85].

Another study carried out by Sharifi-Rad et al. [67] showed that, the *R. persica* leaf extract contained a DPPH radical scavenging activity of 64% at a concentration of 300 µg/mL. Additionally, the ABTS radical scavenging activity of the same *R. persica* leaf extract was measured at 61% at a concentration of 300 µg/mL [67].

In another study led by Tofighi et al. [53], the methanol and ethyl acetate fractions displayed noteworthy antioxidant activities, exhibiting an IC₅₀ value of 0.49 mg/mL [53]. Particularly, the methanol fraction demonstrated exceptional free-radical scavenging activity, with a 91.53% inhibition, comparable to the performance of vitamin E (94.69%) and BHT (90.6%). The ethyl acetate and butanol fractions also exhibited moderate antioxidant activity, with percentages of 81.96% and 81.50%, respectively. The IC₅₀ values for the methanol, butanol, and ethyl acetate fractions were all 0.49 mg/mL. Furthermore, among the pure compounds assessed, chrysoeriol displayed the highest free-radical scavenging activity, surpassing the others and standing on par with vitamin E and BHT in terms of its potent antioxidant activity. Chrysoeriol's antioxidant potential was indeed comparable to that of vitamin E and BHT [53].

Flavonoids like morin and quercetin are known to possess anti-inflammatory properties [86]. These antioxidants are also known to have the ability to mitigate inflammation [87]. Flavonols and tannins exhibit potent antioxidant properties, specifically in terms of free radical scavenging and inhibition of lipid peroxidation [88]. Quercetin offers several beneficial effects on human health, including the reduction of oxidative stress, prevention of diabetes-induced cataracts, and the strengthening of blood vessel integrity [89]. Morin, on the other hand, possesses free-radical-scavenging property [90]. Quercetin also has the ability to eliminate xanthine superoxide and xanthine oxide radicals from the system [91].

7.4. Cytotoxic activity

In the study led by Tahmasebi et al. [78], the methanolic extracts of *R. michauxii* were found to have the lowest IC₅₀ levels: 1.24 mg/mL and 1.23 mg/mL during the vegetative and flowering stages. Thus, the dormant stage had the lowest cytotoxic action (IC₅₀ of 3.2 mg/mL) on MCF-7

breast adenocarcinoma cells, while the flowering/vegetative stages had the highest cytotoxic effects on tumor cells [78].

Cell viability decreased dose-dependently due to the cytotoxic activity of the plant extracts. Compared to the flowering and vegetative stages, the dormant stage had higher levels of cell viability. This extract exhibited the highest level of cytotoxicity during the flowering stage at 3 mg/mL with an inhibition of cell growth of 97.2%. On the other hand, cytotoxicity was the lowest during the dormant stage at 2 mg/mL with a 25.3% inhibition of cell growth. In MCF-7 cells treated with plant extracts, microscopic examination revealed that the vegetative and flowering stages had the most cytotoxic effects and cell death [78].

In another study conducted by Dehghani Nazhvani et al. [77], dichloromethane extract of *R. michauxii* showed IC₅₀ of 0.73, 0.67 and 0.68 mg/mL on oral squamous cell carcinoma cell line after 24, 48, and 72 h [77]. Moreover, the cytotoxic activity of the methanolic extract of *R. michauxii* was evaluated against A-549, HepG-2, MCF-7, MDBK, and WEHI-164 cell lines. The results showed IC₅₀ > 50 (µg/ mL) against the cell lines [80].

In another study led by Safaeian et al. [79], treating human umbilical vein endothelial cells (HUVECs) using *R. persica* extract at concentrations ranging from 50 to 250 µg/mL notably mitigated the cytotoxic impact induced by H₂O₂. The application of *R. persica* extract demonstrated a reduction in hydroperoxide levels and an elevation in ferric reducing antioxidant power (FRAP) values within both intra- and extracellular fluids across varying concentration ranges. This highlights the antioxidative and cell-protective properties of *R. persica* extract in safeguarding HUVEC cells from oxidative stress triggered by H₂O₂. However, *R. persica* extract exhibited cytotoxic effects on HUVECs within the concentration range of 500 to 1000 µg/mL [79]. The presence of potentially toxic compounds, such as labdane-type diterpenoids, could explain the cytotoxic effects observed at higher concentrations of *R. persica* extract [34]. When HUVECs were exposed to *R. persica* extract, a significant reduction in both intra- and extra-cellular hydroperoxides was noted at concentrations ranging from 100 to 250 µg/mL. Additionally, pretreatment of HUVEC cells with *R. persica* extract led to a substantial increase in FRAP levels within intra-cellular fluid at a concentration of 250 µg/mL and in extra-cellular fluid within the range of 25-250 µg/mL. The hydroalcoholic extract of *R. persica* demonstrated effective protection of HUVEC cells against H₂O₂-induced toxicity, particularly within the concentration range of 50-250 µg/mL. This protective effect was also evident in the reduction of hydroperoxide concentration

and the increase in FRAP values in both intra- and extra-cellular fluids. The observed cytoprotective properties of *R. persica* extract against oxidative damage in HUVECs are likely attributed to the high phenolic content and antioxidant activity of its constituent compounds [79]. Flavonoids possess the capability to shield cells from oxidative stress by stimulating cellular defense pathways [92]. Quercetin demonstrated a cytoprotective capacity against oxidative damage induced by H₂O₂ in melanocyte and neuroblastoma cell types [93, 94]. The cytoprotective effect of morin has been confirmed in safeguarding against oxidative damage. This protection is achieved through the activation of extracellular-regulated kinase (ERK) and nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathways, leading to the up-regulation of heme oxygenase-1 [92]. Kaempferol exhibits protective effects against endothelial injury by reducing ROS formation and enhancing nitric oxide production [95]. Additionally, caffeic acid, another antioxidant phenolic compound, can inhibit lipid peroxidation and reduce glutathione depletion, thereby enhancing the cells' resistance to oxidative damage [96]. The cytoprotective activity of *trans*-cinnamic acid against oxidative stress induced by glucose oxidase has been documented in both mouse fibroblast cells and human keratinocyte cells [97]. Isovitexin has the potential to prevent cellular damage caused by ROS through the inhibition of xanthine oxidase [98]. In relation to the reduction of hydroperoxide concentration and the increase in FRAP value within intra- and extra-cellular fluids facilitated by *O. persica* extract, it is plausible that the cytoprotective effect of this herbal extract may involve both direct scavenging of ROS and indirect antioxidant action by enhancing the total antioxidant capacity. The hydroalcoholic extract derived from the aerial parts of *R. persica* has demonstrated the ability to safeguard HUVECs against oxidative damage initiated by H₂O₂ [79].

7.5. Lipid-lowering activity

In an *in vitro* model, *R. michauxii* extracts were evaluated for their ability to lower cholesterol levels [14]. The separated compounds were assessed on the low-density lipoprotein receptors (LDLR) and the proprotein convertase subtilisin/kexin type 9 (PCSK9) in the human hepatocarcinoma cell line Huh7. Some compounds identified in *R. michauxii* extracts significantly lowered intracellular cholesterol. Among them, antirrhinoside exhibited the strongest induction of LDLR and PCSK9. Antirrhinoside lowered cholesterol through a mechanism like statins (as depicted in **Fig. 8**). Antirrhinoside was shown as an effective inducer of low-density lipoprotein receptors (LDLR), resulting in a substantial decrease in intracellular cholesterol levels within

hepatic cells. This suggested new pathways through which iridoids could potentially reduce cholesterol [14].

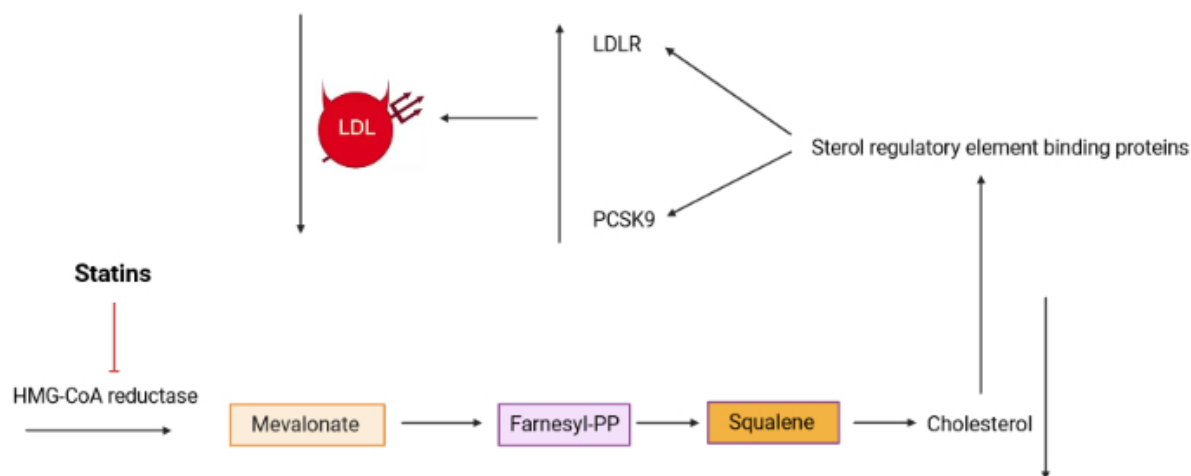


Fig. 8. Mechanism of action of statins in lipid lowering activity

7.6. Antidiabetic activity

Several beneficial properties associated with the hydroalcoholic extract of *R. persica*, including its hepatoprotective potential in conditions like CCL4-induced hepatotoxicity [20], and diabetes [63] were reported. Additionally, the extract exhibited antihypertensive and antioxidant effects [23] as well as nephroprotective function in diabetic rats [62].

The alcoholic extract of *R. persica* was shown to possess potent antidiabetic and blood glucose lowering properties [59]. In diabetic rats, typical symptoms included increased urination, necessitating the cleaning of cages two to three times a day due to the offensive odor. Additionally, water consumption by the rats increased across all groups. However, upon the administration of the plant extract, these symptoms reduced [59].

R. persica contains various essential compounds [48], and these compounds could facilitate mechanisms involving insulin releasor the glucose tolerance factor, as observed in different laboratory animals and humans [99, 100].

The anti-hyperglycemic effects observed could be attributed in part to the reduction of intestinal glucose absorption, an increase in circulating insulin levels (hypoinsulinemia), or the enhancement of peripheral glucose utilization. The oral administration of *R. persica* extract demonstrates significant anti-hyperglycemic actions against streptozotocin-induced hyperglycemia [59].

In the study conducted by Akbarzadeh et al. [57], the effects of the aqueous extract of *R. persica* were evaluated on various parameters in streptozotocin induced diabetic rats, including blood glucose, HDL-C, insulin, pancreas histopathology, total cholesterol, and triglycerides [57]. Throughout the 10th, 20th, and 30th days of the study, fasting blood sugar levels in animals treated with all doses of *R. persica* extract showed a decrease compared to the diabetic control groups. Additionally, on the 30th day of the experiment, the T400 diabetic group exhibited decreased serum triglycerides and improved homeostasis model assessments for insulin resistance when compared to the diabetic control group [57].

Several mechanisms of antidiabetic herbal remedies could involve stimulating the β -cells in the Langerhans islets to enhance insulin secretion and reducing insulin resistance. Phytochemicals such as saponins, have been known to exhibit insulin-like effects and inhibit the formation of glucose in the bloodstream, which can be beneficial in the management of diabetes [101]. The methanolic extract of *R. persica* contains morin and quercetin [50, 84]. Camphorol, isovitexin, morin, and quercetin were identified for their strong antioxidant activity [50]. Some studies suggested that the antidiabetic effect of quercetin in streptozotocin-induced diabetic rats was associated with an increase in insulin absorption and glucose uptake [102]. Quercetin has demonstrated its ability to normalize glucose levels in alloxan-induced diabetic rats and increase liver glycogen levels. Quercetin could reduce hepatic glucose output by affecting hepatic gluconeogenesis and glycogen breakdown. In fact, the effects of quercetin could be similar to those of metformin, a commonly used antidiabetic medication [103]. *R. persica* could reduce serum glucose concentration and insulin resistance. One of the antidiabetic effects of medicinal herbs is the promotion of the growth and number of pancreatic β -cells, as well as the restoration of these cells [104]. Quercetin, a component of *R. persica*, plays a protective role in pancreatic tissue, preventing abnormal compression of Langerhans islets, degeneration, degranulation, and necrotic changes caused by streptozotocin injuries [105]. Consequently, after 30 days of treatment with *R. persica*, the degeneration, degranulation, and necrotic changes in damaged pancreases induced by STZ were reduced and returned to a normal state. *R. persica* prevented the loss of β -cells and regulated serum lipid and sugar levels in diabetic animals by reducing insulin resistance, lowering serum glucose concentration, and improving insulin function [57].

The aerial parts of *R. persica* have been evaluated for their antioxidant and antiglycation properties [24]. 3',7-Dihydroxy-4',6,8-trimethoxy-flavone was isolated from *R. persica* for its antiglycation

properties [24]. This compound exhibited significant antiglycation activity, with a 65% inhibition observed at a concentration of 3 mM. Comparatively, the standard inhibitor rutin showed 83% inhibition. These findings suggest that *R. persica* and its constituents may be useful in mitigating the effects of glycation and advanced glycation end products formation, which are implicated in diabetic complications.

In another study led by Manzari-Tavakoli et al. [54], the application of *R. persica* extract resulted in a significant reduction of serum glucose levels in diabetic rats, concomitant with a simultaneous increase in serum insulin levels [54]. Furthermore, this extract demonstrated a capacity to enhance glucose-induced insulin secretion in C187 β -cells. Additionally, in diabetic rats, the plant extract exhibited a significant reduction in malondialdehyde (MDA) levels and a substantial increase in glutathione levels within the liver. These findings highlight the multifaceted therapeutic attributes of *R. persica* shoot extract, encompassing its antihyperglycemic, anti-lipid peroxidation, and insulin secretory properties [54].

Oral administration of the methanolic extract derived from *R. persica* could lead to a reduction in serum glucose levels in diabetic rats [62-65]. This effect appeared to be partially mediated through two mechanisms: the stimulation of insulin release and improvements in pancreas tissue. There is a growing body of evidence that suggests that certain antidiabetic plants can enhance circulating insulin levels [106]. However, the antihyperglycemic properties of this extract may also involve extra pancreatic actions. These actions could potentially include the stimulation of glucose utilization in peripheral tissues, modulation of hormones that regulate carbohydrate metabolism (such as glucagon and growth hormone), or the inhibition of the proximal tubular reabsorption mechanism for glucose in the kidneys. Given the promising therapeutic potential of *R. persica* in treating metabolic disorders such as diabetes, there is a growing interest in glucosidase inhibitors [107]. Both the aqueous and methanolic extracts of *R. persica* exhibited an inhibitory effect on α -glucosidase, with an inhibition rate of less than 25% [108]. Additionally, the findings of another study confirmed the α -glucosidase inhibition by the *R. persica* extract [109].

Moreover, the induction of diabetes in rats using streptozotocin is known to result in high oxidative stress due to prolonged and chronic hyperglycemia. This condition leads to a depletion of the enzymes involved in the antioxidative defense system, thereby promoting the generation of free radicals [110].

Flavonoids and tannins, as well as triterpenoids and various secondary plant metabolites, exhibited hypoglycemic effects in diverse experimental animal models [111, 112].

Quercetin, demonstrated the ability to prevent and protect against streptozotocin-induced oxidative stress and beta-cell damage in the pancreas of rats [112].

Additionally, quercetin could increase blood insulin levels and elevate serum calcium (Ca^{2+}) and magnesium (Mg^{2+}) levels [113]. Certain flavonoids have shown strong inhibitory effects on specific metabolic enzymes like cyclooxygenase, lipooxygenase, monoamine oxidase, and xanthine oxidase, which are known to generate free radical products within the body [114]. Morin, for instance, is a potent inhibitor of urate reabsorption in the kidneys and also exhibits inhibitory effects on xanthine oxidase [115]. Moreover, quercetin could also ameliorate the adverse effects of diabetes mellitus (DM) on liver tissue, particularly in diabetic patients with concurrent hepatic diseases [116]. Quercetin supplementation was shown to improve the diabetic condition in rats [117] and reduce oxidative stress within the liver of streptozotocin-induced diabetic rats [112, 118].

R. persica has emerged as a promising and safe alternative medicine for managing blood sugar levels in individuals with diabetes [58]. Notably, it was demonstrated that the aqueous root extract of *R. persica* significantly reduced triglyceride, total cholesterol, LDL-C (low-density lipoprotein cholesterol), and increased HDL-C (high-density lipoprotein cholesterol) levels when compared to normal, control, and metformin-treated groups. This extract displayed particular efficacy in lowering serum total cholesterol, triglycerides, and LDL-C in hyperlipidemic diabetic rats [58].

A methanol fraction of *R. persica* exhibited effects comparable to glibenclamide and insulin. The EC_{50} (half-maximal effective concentration) of the methanol fraction was found to be 307.12 mg. Furthermore, the aqueous infusion extract significantly reduced blood glucose levels in diabetic mice, with no significant difference observed between this fraction and glibenclamide or insulin. The EC_{50} of the methanol fraction again measured at 307.12 mg [53]. These findings indicated that both the aqueous infusion extract and methanol fraction had hypoglycemic effects, although differences between the two suggested the presence of different phytochemicals. These results supported the traditional use of this herb in folk medicine as an hypoglycemic agent [53]. The observed antidiabetic effects in the methanol fraction of *R. persica* could be attributed to the presence of one or more synergistic antihyperglycemic compounds. Within this fraction, the abundance of phenolic compounds and flavonoids stood out, and these compounds are well-known

as potent antihyperglycemic agents. These compounds could demonstrate the ability to regenerate damaged beta cells in alloxan-induced diabetic rats [119, 120].

Flavonoids, in particular, are notable for their versatility as antidiabetic agents, given their capacity to facilitate both glucose-lowering actions (insulin-mimetic effects) and insulin secretion (insulin secretagogue effects) [121]. Among the flavonoids found in *R. persica*, morin and quercetin could be such flavonoids because of their potent antioxidant properties [122].

Quercetin displayed inhibition of glucose and fructose transport through intestinal cell GLUT2 transporters [123]. Furthermore, it enhanced insulin secretion in response to glucose and provided protective effects against oxidative damage to beta cells induced by hydrogen peroxide [124]. These protective effects could be attributed to quercetin's ability to increase glucokinase activity, a pivotal enzyme in glucose metabolism [125]. Collectively, these underscored its potential in promoting glucose regulation and mitigating diabetes-related complications.

The administration of morin showed potential in ameliorating various aspects of hyperglycemia, including glucose intolerance, lipid peroxidation, and insulin resistance [126-128].

This compound could enhance insulin receptor signaling, reduce hyperglycemia, and mitigate lipid deposition in the livers of diabetic rats, underscoring its dual role as an antidiabetic and antioxidant agent [129, 130]. Another study demonstrated that morin administration led to increased insulin receptor activation while decreasing gluconeogenesis potency [131]. Apigenin derivatives and chrysoeriol could also lower blood glucose levels in diabetic animals [132, 133].

In the case of *R. persica* extract, oral administration to diabetic rats for 14 d reduced serum glucose levels. Notably, it significantly increased insulin serum levels. Moreover, the plant extract exhibited a positive impact on pancreas tissue, increasing the number of islets in all doses and, enhancing the mean diameter of the islets. These findings collectively suggest that *R. persica* extract exerts a hypoglycemic effect by improving pancreatic islets and promoting insulin secretion [65].

The treatment of diabetic rats with *R. persica* extract reduced glucose serum levels, as well as cholesterol and triglycerides serum levels. The extract demonstrated greater efficacy in reducing glucose and triglycerides serum levels in diabetic rats compared to glibenclamide. These findings highlighted the antihyperglycemic and antihyperlipidemic properties of *R. persica* extract in the context of diabetes management in rat models [64].

Interestingly, *R. persica* extract not only significantly reduced serum glucose levels but also reversed them to levels like the control group. Additionally, alkaline phosphatase activity was notably increased in all experimental groups compared to the control group [60].

In the diabetic group, several noteworthy changes were observed, including elevated serum glucose levels, decreased levels of luteinizing hormone (LH) and testosterone, as well as reductions in testis and epididymis weight when treated with *R. persica* [66]. Furthermore, diabetic rats exhibited a significant increase in oxidant factors and a decrease in antioxidant factors. Additionally, they had significantly lower levels of serum testosterone and luteinizing hormone when compared to the control group. These findings collectively indicated that *R. persica* powder possesses antioxidant properties that benefit the testis and epididymis tissues in diabetic rats. Moreover, it improves the histological structure of the testicles in diabetic rats, underscoring the protective potential of *R. persica* against reproductive complications induced by diabetes in male rats. The study highlights the protective effects of *R. persica* in mitigating oxidative stress and the changes in testosterone and serum luteinizing hormone levels induced by diabetes [66].

Oxidative stress can contribute to various diabetic complications, further underscoring the importance of antioxidants like those found in *R. persica* in mitigating these effects. The oral administration of *R. persica* extract to the treated diabetic group demonstrated a significant and dose-dependent hypoglycemic effect in streptozotocin-induced diabetic rats when compared to the corresponding diabetic rats [61]. Notably, the level of insulin in the diabetic group was significantly higher than in the treated diabetic group that received the extract. An analysis of the data revealed a significant increase in the volume of beta cells in both the diabetic group (approximately 34%) and the treated diabetic group (approximately 11%) in comparison to the control group. The difference in beta cell and its nuclei volume between the diabetic and treated diabetic groups was also significant. The results suggested that *R. persica* extract could play an effective role in managing diabetes by controlling hyperglycemia without stimulating the beta cells to increase insulin secretion. This approach might help prevent the remaining beta cells from undergoing pathological changes such as hypertrophy. The study further demonstrated that blood glucose levels decreased in the treated diabetic group that received daily oral administration of *R. persica* extract when compared to the diabetic group.

Moreover, the investigation revealed hypertrophic changes in beta cells and beta cell nuclei in both the diabetic and treated diabetic groups in comparison to the control group. However, hypertrophic

changes in the treated diabetic group were significantly less pronounced than those in the diabetic group. These findings indicated that *R. persica* extract had antidiabetogenic efficacy in streptozotocin-induced diabetic rats. It effectively controlled hyperglycemia and prevented the remaining beta cells in pancreatic islets from undergoing pathological changes, particularly hypertrophy [61]. The mechanisms underlying these anti-hyperglycemic effects may involve systemic factors such as the reduction of intestinal glucose absorption, enhanced peripheral utilization of glucose, modulation of insulin release and activity, or the involvement of glucose tolerance factors. These effects align with the broader body of evidence showing the beneficial impact of medicinal plants in various laboratory animals and human beings [99, 100]. The *in vitro* α -glucosidase inhibitory potential of the ethyl acetate fraction of the ethanol extract of *R. persica* was studied [51]. Additionally, *in silico* analyses were conducted to assess the inhibition potentials of isolated compounds on acetylcholine esterase and α -glucosidase. The spiro-diterpenes identified in *R. persica* displayed promising α -glucosidase inhibitory activity based on docking studies. Effective management of hyperglycemia involves inhibiting the α -glucosidase enzyme, which hinders the release of α -glucose from carbohydrates. This inhibition leads to delayed digestion of oligo carbohydrates, resulting in reduced glucose absorption and subsequently lower blood sugar levels [134]. The ethyl acetate fraction of *R. persica* exhibited α -amylase inhibition at a rate of 99.39%, similar to acarbose, a standard medication [135]. Furthermore, the ethanolic extract of *R. persica* demonstrated α -amylase inhibitory effects, reaching 96.7% [136]. α -Amylase is a critical enzyme in the human digestive system, pivotal for converting starch into glucose and facilitating its absorption [137]. The antioxidant compounds found in the methanolic extract of *R. persica* could contribute to the restoration of Langerhans islets, enhancing insulin secretion, and reducing serum glucose levels [136, 138]. An investigation into the antidiabetic properties of *R. persica* by [74] in mice revealed that the methanol fraction exhibited an effect comparable to that of glibenclamide and neutral protamine Hagedorn insulin. These treatments effectively reduced blood sugar levels in mice.

Antidiabetic mechanisms of *R. persica* and its main compounds are summarized in **Fig. 9**.

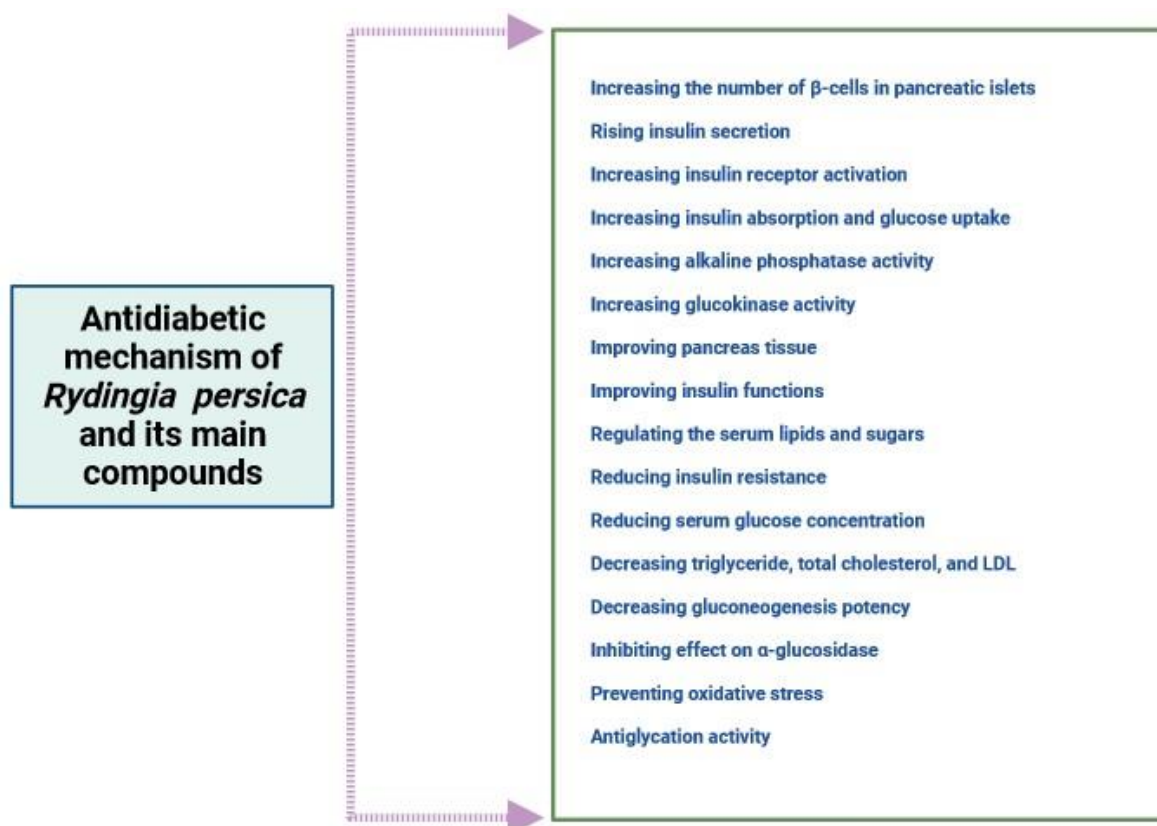


Fig. 9. Antidiabetic mechanisms of *Rydingia persica* and its main compounds

7.7. Atherosclerosis complication

Both quercetin and the hydroalcoholic extract of *R. persica* demonstrated serum lipids lowering effect (excluding HDL), and reducing effect on oxidative stress factors, aorta contraction, blood pressure, and weight gain. These interventions led to improvements in vascular structure and have effectively prevented the formation of arterial plaques through their antioxidant activities. Quercetin and the *R. persica* extract were more effective than atorvastatin in increasing serum HDL levels and decreasing serum levels of MDA, signifying their potential as promising agents for the prevention of atherosclerosis [55]. Serum levels of LDL, MDA, ROS, and total cholesterol (TC) were significantly lower in the experimental groups compared to the sham group. Additionally, there was a decrease in serum MDA levels in these two groups when compared to the atorvastatin-treated group. Furthermore, blood pressure parameters significantly decreased in rats treated with quercetin and the hydroalcoholic extract in comparison to the sham group. These findings demonstrated the potential therapeutic benefits of quercetin and *R. persica* extract in

preventing and managing cardiovascular complications and atherosclerosis [55]. The findings from these studies offered a promising avenue for the treatment of atherosclerosis, a condition characterized by the thickening of the intima-media layer of arteries and is a precursor to cardiovascular diseases [139]. Previous research established a link between obesity, hypercholesterolemia, and the increased production of free radicals, leading to oxidative stress. Hypercholesterolemia can elevate the activity of oxidant enzymes, resulting in cellular damage. This increased enzyme activity in hypercholesterolemia also amplifies the activity of ROS and promotes the generation of hydroxyl radicals. Additionally, the elevated levels of triglycerides in obese rats contribute to an imbalance between oxidants and antioxidants [140]. Quercetin was shown promise in ameliorating atherosclerosis symptoms, by reducing lipid levels, inhibiting lipid oxidation, and mitigating total weight gain. It was associated with the reduction of oxidative enzyme activity, as documented in previous studies [141]. Both atorvastatin, quercetin, and the hydroalcoholic extract of *R. persica* improved atherosclerosis by reducing serum levels of LDL and cholesterol. Furthermore, these interventions significantly decreased the levels of oxidative stress enzymes, specifically MDA and ROS. The quercetin-treated group exhibited a reduction in oxidative enzyme levels, an increase in HDL levels, and a decrease in LDL serum levels. Both quercetin and the hydroalcoholic extract also led to a significant decrease in systolic, diastolic, mean arterial, and pulse pressure [55].

Statins, such as atorvastatin, could contribute to antihypertensive effects by reducing pulse rate, potentially stemming from lower arterial contraction due to increased nitric oxide bioavailability, enhanced endothelial-dependent vasodilation, and decreased endothelin-1 concentrations. Statins might also act as inhibitors of the renin-angiotensin-aldosterone system (RAAS), blocking intracellular pathways associated with angiotensin II and reducing the expression of type 1 angiotensin receptors, which could lead to a reduction in blood pressure [142]. These mechanisms further support the potential of statins and compounds like quercetin in managing cardiovascular complications, including atherosclerosis and hypertension.

7.8. Anticonvulsant activity

The anticonvulsant activity of *R. persica* total extract was assessed using a mouse model induced by pentylenetetrazole (PTZ), with diazepam as a reference drug. Mechanistic investigations included the use of flumazenil, a GABAA-benzodiazepine receptor complex site antagonist. The

results demonstrated that the extract provided protection against convulsions with a level of protection comparable to that of benzodiazepine. Specifically, at this dose, the extract conferred a significant 93.75% protection rate [56]. Moreover, the mean clonic seizure latency in mice treated with the plant extract, administered either 30 min or 60 min before PTZ injection, showed statistically significant differences from the control group. In both instances, the extract provided substantial protection, with rates of 93.75% and 93.05%, respectively [56]. The extract effectively suppressed the onset and duration of clonic seizures in the PTZ model, and this anticonvulsant effect appeared to be dose dependent. The study investigated the impact of flumazenil, a selective antagonist of the benzodiazepine receptor site within the GABAA-BZD receptor complex. When flumazenil (0.5 mg/kg) was administered 5 minutes prior to the extract, it reversed the effect of the extract in prolonging seizure latency. This finding suggested that the anticonvulsant effect of the extract could be linked to the activation of the benzodiazepine receptor. Notably, diterpenes present in *R. persica* were previously identified as having sedative effects on the central nervous system, including protection against PTZ and electroshock-induced convulsions in mice [143, 144]. In another study, the molecular docking study revealed the morin compound isolated from *R. persica* with high negative docking energy on the receptors N-Methyl-D-aspartic acid and amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [145]. The mechanisms of these receptors influence the majority of anticonvulsant drugs [146, 147].

Consequently, it was concluded that the anticonvulsant activity of *R. persica* extract could be attributed, at least in part, to its significant diterpene content. These research findings not only supported the traditional medicinal use of *R. persica* for epilepsy management but also underscored its potential as an anticonvulsant agent [56].

7.9. Antihypertensive activity

The antihypertensive effect of the hydroalcoholic extract obtained from the aerial parts of *R. persica* was investigated in an animal model of dexamethasone (Dex)-induced hypertension [23]. The results demonstrated several significant outcomes:

- Oral administration of *R. persica* extract effectively prevented and dose-dependently reversed the increase in systolic blood pressure (SBP) induced by Dex.

• Pre-treatment with *R. persica* extract reduced the concentration of plasma hydrogen peroxide and increased the levels of plasma ferric reducing antioxidant power, indicating an antioxidant effect.

• The administration of *R. persica* extract prevented the loss of body weight typically observed in Dex-induced hypertension.

These findings suggested that *R. persica* extract had antihypertensive properties in the context of Dex-induced hypertension. Furthermore, the study explored the potential role of major terpenoids found in the aerial parts of *R. persica*, including α -pinene, linalool, and verbenol, in contributing to its antihypertensive effects.

Phenolic compounds, particularly flavonols, have been associated with various protective effects on the cardiovascular system, including antioxidant, anti-inflammatory, vasorelaxant, antihypertensive, and anti-atherogenic effects [148]. Quercetin, was demonstrated to possess antihypertensive effects in animal models of hypertension and in hypertensive patients [149]. Its beneficial actions include protection of nitric oxide and endothelial function, endothelium-independent vasodilation, inhibition of LDL oxidation and platelet aggregation, reduction of adhesion molecules and other inflammatory markers, and prevention of structural and functional changes in the cardiovascular system under conditions of oxidative stress and ischemia [148, 149]. Additionally, other flavonols like kaempferol and morin could display antioxidant and antihypertensive properties. Kaempferol could protect endothelial cells from damage, reduce ROS production in aortic endothelial cells, and enhance nitric oxide production [95], while morin, could show antioxidant and antihypertensive effects, as evidenced by its ability to reduce blood pressure, heart rate, and prevent organ hypertrophy in hypertensive rats. This might be due to morin-induced inhibition of lipid peroxidation and restoration of the activity of enzymes that scavenge free radicals [150].

Furthermore, terpenoids like α -pinene and linalool could be linked to vasorelaxant, hypotensive, and antioxidant effects [151].

The antioxidant properties of *R. persica* extract, as demonstrated by its ability to reduce plasma H₂O₂ levels and enhance total antioxidant capacity, likely contribute to its antihypertensive effects in the Dex-induced hypertension model [23]. These findings provided valuable insights into the potential therapeutic benefits of *R. persica* in managing hypertension and its associated oxidative stress.

7.10. Bone protective effects

The potential bone-protective effects of *R. persica* ethanolic extract in streptozotocin-induced diabetic rats was investigated [76]. Their results revealed several key findings:

- Administration of 300 mg/kg of *R. persica* extract effectively reduced serum glucose levels in the diabetic rats.
- In the streptozotocin group, parameters such as epiphyseal and metaphyseal trabecular thickness, as well as epiphyseal bone area/tissue area, were significantly decreased, indicating bone deterioration.
- Treatment with *R. persica* extract at a dosage of 200 mg/kg reversed all these bone-related parameters to levels comparable to those of the control group.
- Additionally, marrow area/cortical area in rats treated with 450 mg/kg of *R. persica* extract showed the highest values among the groups, further supporting the bone-protective effects of the extract.

Overall, the findings demonstrated that the ethanolic extract of *R. persica* had bone-protective effects in streptozotocin-induced diabetic rats. Importantly, these effects were observed independently of the extract's ability to lower glucose levels.

Similar study highlighted the potential involvement of mechanisms beyond the direct amelioration of hyperglycemia in the bone-protective properties of *R. persica* extract in diabetic rats [60].

Considering the known role of oxidative stress in diabetes-induced bone loss, particularly its negative impact on bone formation by osteoblasts, the antioxidant properties of *R. persica* extract might play a significant role in these bone-protective effects [152]. This suggested that the ability of the extract to combat oxidative stress could be a key factor in preserving bone health in diabetic individuals [36, 54].

7.11. Anti-sclerotic effect

Hypercholesterolemia is now recognized as a major risk factor for the development of atherosclerosis, a condition that plays a significant role in mortality rates in both developed and certain developing countries, such as Iran [153]. The pathogenesis of atherosclerosis is complex, with evidence suggesting that the oxidation of lipids and LDL is a critical step in the formation of atherosclerotic plaques.

Rahdari et al. [75] investigated the potential anti-hypercholesterolemic and antiatherogenic effects of the ethanolic extracts derived from *R. persica* in an animal model of high-fat diet-induced hypercholesterolemia. Their study revealed several important findings:

- Treatment with ethanolic extracts of *R. persica* in hypercholesterolemic rats did not result in significant changes in cholesterol, triglyceride, or LDL or HDL levels.
- However, the extracts did lead to a significant decrease in the levels of inflammatory factors, including IL-6, PLA2, and CRP.
- The ethanolic extracts of *R. persica* were found to have anti-atherosclerotic effects, primarily attributed to their ability to reduce inflammatory factors and PLA2 activity.
- It is suggested that the reduction in PLA2 activity by *R. persica* may be due to the presence of flavonoid compounds, such as β -sitosterol or eugenol compounds, which can inhibit the enzyme cyclooxygenase-2.
- The study also indicates that *R. persica* may lower the inflammatory factor CRP levels due to its abundant content of flavonoids and phenolics.

These findings showed the potential therapeutic benefits of *R. persica* in mitigating the inflammatory processes associated with atherosclerosis, even though it might not directly impact cholesterol and lipid levels. The ability of *R. persica* to modulate inflammatory factors and PLA2 activity highlights its potential role in preventing or managing atherosclerosis and related cardiovascular complications.

7.12. Anti-ischemia/reperfusion injury

Circulatory challenges characterized by ischemia tend to recur frequently in diabetic patients, and scientific evidence established the multifaceted impact of ischemia-reperfusion, affecting not only local tissues but also distant organs [68, 154]. Notably, within the context of renal biology, where the regulation of blood flow undergoes significant alteration post-ischemia, renal ischemia/reperfusion (I/R) emerged as a prominent instigator of acute renal failure. The pathophysiology of renal I/R is intricately intertwined with the generation of oxygen radicals and oxidative stress, stemming from an imbalance between the production of ROS and the antioxidant capacity, as elucidated by [155]. In normal and diabetic rat subjects, I/R resulted in a substantial elevation in serum levels of urea and creatinine [156]. Furthermore, renal I/R induced a marked increase in concentrations of MDA, myeloperoxidase, and nitric oxide, accompanied by a significant reduction in the activities of superoxide dismutase and catalase, in stark contrast to the

sham-operated group. Notably, diabetic rats exposed to renal I/R displayed an even more pronounced exacerbation of these parameters, coupled with a further decline in antioxidant enzyme levels when compared to their nondiabetic counterparts [156].

Prominently, pre-treatment with *R. persica* extract demonstrated its capacity to ameliorate the deleterious consequences of renal I/R in diabetic rats. This compelling evidence suggested that *R. persica* extract could hold promise as a therapeutic intervention to safeguard against renal injury precipitated by ischemia-reperfusion in diabetic individuals [156].

In another study led by Takhtfooladi et al. [68], the administration of *R. persica* extract significantly ameliorated the decrease in glomerular filtration rate induced by reperfusion, leading to notable reductions in serum urea and creatinine concentrations. In contrast, urinary creatinine levels were significantly diminished in the ischemia-reperfusion group compared to other groups. Additionally, animals experiencing reperfusion injury exhibited notable increases in urinary excretion rate, water intake, and the ratio of kidney/body weight compared to other experimental groups [68].

Histological examination revealed that rats pretreated with *R. persica* extract displayed normal kidney morphology. Furthermore, skeletal muscle ischemia-reperfusion resulted in a significant elevation in renal tissue MDA levels, a marker of oxidative stress. However, pretreatment with *R. persica* extract was associated with lower MDA levels. Moreover, hindlimb ischemia-reperfusion led to significant decreases in renal tissue catalase and superoxide dismutase activity, as well as glutathione levels. Remarkably, pretreatment with *R. persica* extract mitigated these declines, indicating its potential in enhancing antioxidant defenses [68].

Pre-treatment with *R. persica* extract provided significant protection against renal injury induced by skeletal muscle ischemia-reperfusion. These results supported the notion that *R. persica* might play a pivotal role in attenuating remote renal injury following skeletal muscle ischemia-reperfusion in an animal model, potentially through its antioxidant and free radical scavenging activities [68].

7.13. Morphine withdrawal

Both oral and intraperitoneal administration of the hydroalcoholic extract of *R. persica* yielded a reduction in withdrawal symptoms [82]. The hydroalcoholic extract significantly alleviated withdrawal signs, including diarrhea, piloerection, tremor, and ptosis. The *n*-hexane extract demonstrated notable inhibition of diarrhea only.

These findings suggested that *R. persica* extract had constituents that could effectively mitigate morphine withdrawal syndrome [82]. Additionally, the results strongly indicated that the components of the hydroalcoholic extract of *R. persica* could alleviate morphine withdrawal syndrome. This plant contains flavonoids and it is plausible that these flavonoids could contribute to the observed pharmacological effects [82]. It is noteworthy that previous reports suggested that flavonoids could suppress opioid withdrawal syndrome [157], underscoring their potential significance in addressing drug dependence-related issues.

7.14. Hepatoprotective activity

Carbon tetrachloride (CCl₄) is renowned as one of the most potent hepatotoxins, capable of inducing severe liver damage through the generation of highly reactive free radicals. This toxic compound can lead to a spectrum of liver injuries, including centrilobular steatosis, inflammation, apoptosis, and cell necrosis [158, 159]. However, there is promising evidence to suggest that the administration of *R. persica* ethanolic extract significantly mitigated the elevation of serum enzyme markers induced by CCl₄. These results demonstrated the potential of *R. persica* extract to alleviate the oxidative stress induced by CCl₄ exposure. Moreover, treatment with *R. persica* extract at varying doses resulted in a reduction in enzyme markers, bilirubin levels, and the marker of lipid peroxidation (MDA), along with an increase in total protein and albumin levels [20]. Complementary pathological examinations further supported the hepatoprotective effects of *R. persica* extract, with a clear dose-dependent trend. The hepatic lesions induced by CCl₄ were notably ameliorated by *R. persica* extract, with the most pronounced protection observed at the 80 mg/kg dose. Liver sections from this group exhibited minor patho-morphological changes, resembling those of the control group [20].

In essence, *R. persica* extract showed promise as an effective agent for preventing CCl₄-induced hepatic damage in rats, indicating its potential as a hepatoprotective agent. These protective effects against liver damage may be attributed, at least in part, to its ability to scavenge free radicals, inhibit lipid peroxidation, and enhance antioxidant activity [20].

The hepatoprotective potential of methanolic extract derived from the aerial parts (shoots) of *R. persica* was investigated against CCl₄-induced acute hepatotoxicity in male rats [81]. Their findings revealed that the methanolic extract exhibited significant hepatoprotective and antioxidant properties. This was further substantiated by histopathological examinations, confirming its efficacy in preventing acute liver damage. The protective mechanisms of the methanolic extract

against CCl₄-induced acute liver damage appeared to involve a reduction in lipid peroxidation, evidenced by decreased MDA levels and increased glutathione content.

Notably, antioxidants play a pivotal role in shielding living organisms from the harmful effects of substances like CCl₄ and carcinogens [160].

7.15. Burn wound healing

The process of healing burn wounds is intricate and involves re-epithelialization, the formation of granulation tissue, and the remodeling of the burn site [161]. The potential of the methanolic extract of *R. persica* in expediting the burn wound healing process, (owing to its anti-inflammatory and antioxidant properties) was investigated [22]. On the fifth day of the experiment, a significant reduction in inflammation in the burn area when compared to the control group, indicating that the methanolic extract of *R. persica* effectively suppressed inflammation was observed [22]. Subsequently, from day 5 to day 14, there was a peak in fibroblast proliferation, accompanied by an increase in collagen accumulation. Angiogenesis, the formation of new blood vessels, showed greater improvement in group III, facilitating re-epithelialization. In this group, an ointment containing *R. persica* extract was applied twice daily. By day 5, in all groups, burn-induced damage to the skin was apparent, but in group III, the formation of new blood vessels was observed. The difference in angiogenesis between the control group and group III was statistically significant. The control group exhibited an indistinct epithelium, with the dermal layer being half the thickness of the adjacent unburned region [22].

By day 14, group III displayed the most favorable burn healing results among all the groups. Group I exhibited wounds covered with a thick layer of scar tissue. In contrast, skin sections from groups II and III exhibited a multilayered epithelium. By day 21, groups II and III displayed well-organized epidermal layers and increased epidermal thickness. In the control group, the dermal compartment exhibited irregularities [22].

The topical application of the methanolic extract of *R. persica* on rats demonstrated significant wound-healing activity [22]. The treatment with *R. persica* extract might prevent neutrophil-dependent tissue damage and oxidative injury caused by burns [22]. Flavonoids, like morin, have been known to promote the wound-healing process by enhancing the strength of collagen fibers, increasing circulation, promoting DNA synthesis, and reducing lipid peroxidation [162]. Morin in *R. persica*, is renowned for its anti-allergic, anticancer, anti-inflammatory, antimutation, and antioxidant properties [126].

Labdane-type diterpenoids isolated from *R. persica* induced the expression of tight-junction proteins, claudin-1 and occludin and inhibited the release inhibition of pro-inflammatory cytokines, that might improve tissue regeneration in wound-healing process [163].

The methanolic extract of *R. persica* possesses anti-inflammatory and antioxidant properties, which could play a crucial role in promoting the healing of burn wounds [164].

The composition of the methanolic extract of *R. persica*, coupled with [22] the observations regarding dermal regeneration, unequivocally supported the extract's beneficial impact on cellular proliferation, the formation of granulation tissue, and the overall process of epithelialization.

7.16. Anti-inflammatory activity

The antinociceptive and anti-inflammatory properties of different fractions of *R. persica* extract were investigated [21]. The ethyl acetate (EA) and *n*-butanol (BU) fractions at a dose of 100 mg/kg, as well as the methanolic (ME) fraction at doses of 100 and 200 mg/kg, exhibited a significant difference compared to the control group during the second phase of the formalin test, indicating their noteworthy anti-nociceptive effects. Notably, the ME fraction displayed superior analgesic effects compared to indomethacin, with an IC₅₀ value of 85.87 mg/kg [21].

In the anti-inflammatory investigation, EA fraction failed to reduce rat paw edema after 6 hours, while ME and BU fractions, selected for further analysis, demonstrated significant anti-inflammatory activities comparable to indomethacin after the same time frame. There was no clear dose-dependent trend in the anti-inflammatory activity of the ME fraction [21].

The study proposed that the mechanism of action of *R. persica* fractions might differ from that of indomethacin, and they might not inhibit cyclooxygenase-2 (COX-2) within the first 4 h of the experiment. However, after 4 to 5 h, ME fraction at doses of 200 and 400 mg/kg exhibited anti-inflammatory activity comparable to indomethacin. BU and ME fractions displayed responses similar to indomethacin after 6 h, suggesting a potential role as selective inhibitors of inducible nitric oxide synthase (iNOS) [21].

These findings align with previous reports on the anti-inflammatory effects of flavonoids [165, 166], highlighting their potential in inhibiting factors like nuclear factor-kappa B (NF-κB) and signal transducer and activator of transcription 1 (STAT-1), critical for iNOS activation. Flavonoids such as apigenin, isorhamnetin, kaempferol, and quercetin have been shown to inhibit NF-κB and STAT-1 activation [167, 168], and some of them also inhibit COX-2 expression [169, 170].

R. persica exhibited both antinociceptive and anti-inflammatory effects, resembling the actions of various nonsteroidal anti-inflammatory drugs. The presence of flavonoids in the ME fraction of *R. persica* is believed to play a pivotal role in inhibiting the expression of COX-2 and iNOS, contributing to its anti-nociceptive and anti-inflammatory properties [21]. The anti-inflammatory activity of the *R. persica* leaf extract has been shown previously [21, 67]. It has been shown that labdane-type diterpenoids are involved in anti-inflammatory property of *R. persica* by the inhibition of IL-6, TNF- α release, and nitrotyrosine formation [163].

Anti-nociceptive activity of *R. persica* extract was studied and all fractions of *R. persica* extract exhibited analgesic effects similar to indomethacin (first phase of the experiment), which served as the positive control [21]. However, during the second phase, notable differences were observed between the normal saline group and the groups treated with EA, BU fractions, and ME fractions. Remarkably, the ME fraction displayed superior analgesic effects compared to indomethacin, with an IC₅₀ value of 85.87 mg/kg [21].

It was found that in the first phase, they did not exhibit inhibitory activity on peripheral nociception. However, in the second phase, BU, EA, and ME fractions of *R. persica* demonstrated antinociceptive effects, suggesting that the analgesic actions of these fractions are mediated centrally through the release of neurotransmitters [21].

7.17. Renoprotective activity

Nephrotoxicity is a significant concern associated with vancomycin (VCM), a glycopeptide antibiotic, and it is characterized by the involvement of free radicals in its pathophysiology [171]. In an effort to mitigate VCM-induced nephrotoxicity in rats, the impact of the hydro-alcoholic extract of *R. persica* was investigated [83].

R. persica demonstrated a reduction in the elevation of serum levels of urea, creatinine, and MDA, akin to the effects of vitamin E. Furthermore, *R. persica* significantly reduced the presence of red blood cells (RBC) in urine. The plant extract contributed to the improvement of creatinine clearance and the proportion of kidney weight to body weight. These biochemical findings were corroborated by pathological observations [83]. Histopathological examinations further confirmed that VCM injection had induced renal injury characterized by interstitial edema, tubular swelling, and inflammatory infiltrate. However, many of these histopathological alterations were ameliorated by *R. persica*. Notably, the kidney specimens from animals that received *R. persica* displayed noticeable improvements in histological assessment [83].

These results collectively support the notion that *R. persica* possesses beneficial properties for mitigating VCM-induced nephrotoxicity in rats, attributable to its antioxidant attributes. There is a growing body of evidence suggesting that the generation of ROS and inflammation plays a pivotal role in VCM-induced renal toxicity [172, 173].

The protective role of antioxidants in mitigating the nephrotoxicity of VCM was previously studied [174]. It was hypothesized that *R. persica* could exert its nephroprotective effects by inhibiting the production of free radicals and reducing lipid peroxidation, as evidenced by the decrease in MDA levels. This hypothesis aligned with the recognized role of free radicals in the development of VCM-induced nephrotoxicity [81] and the antioxidant properties of *R. persica*, as demonstrated in previous studies [50, 175].

R. persica has flavonoids like isovitexin, kaempferol, morin, and quercetin, which exhibit substantial antioxidant activities comparable to that of butylated hydroxyl anisole and vitamin E [122]. Notably, quercetin exerts its antioxidant effects by inhibiting lipid peroxidation through the blockade of xanthine oxidase enzyme [176]. Additionally, this flavonol directly scavenges hydroxyl and superoxide radicals [177]. Morin, another flavonoid of *R. persica*, also has potent antioxidant activity [178] and can inhibit xanthine oxidase [179], as well as cyclooxygenase and lipoxygenase [180].

8. Conclusion and future perspectives

The Iranian *Rydingia* species, *R. michauxii* and *R. persica*, possess remarkable phytochemical diversity and therapeutic potential, as explored in this comprehensive review. These plants have deep roots in traditional Iranian medicine and are rich repositories of bioactive compounds with wide-ranging pharmacological properties. The essential oils of these species are characterized by a blend of monoterpenes, sesquiterpenes, and phenylpropanoids, with major constituents such as α -pinene, carvacrol, caryophyllene oxide, dillapiole, eugenol, hexadecanoic acid, and pentacosane. The wide variety of plant chemicals in *Rydingia* species has led to their use in traditional Iranian medicine for a range of health issues, with scientific studies backing up their effectiveness. However, turning these traditional remedies into clinically accepted treatments is still a long way off. To unlock the therapeutic potential of *Rydingia* and develop commercially available drugs, a focused effort is required. Extensive clinical trials are needed to confirm the safety and effectiveness of these plant-derived compounds and to understand their mechanisms of action in

the body. Exploring synergistic interactions among major bioactive constituents could also lead to new ways of enhancing their therapeutic effects. Additionally, synthesizing analogues of promising natural products could improve their drug-like properties and pave the way for more efficient and targeted therapies. Interdisciplinary research is essential to unlock the full therapeutic potential of these plants and advance global healthcare.

Author Contributions: Conceptualization, A.T., L.N. and C.W.L.; methodology, A.T., B.J. and V.A.; writing—original draft preparation, A.T., B.J., L.N. and V.A.; writing—review and editing, A.T., C.W.L. L.N., S.D.S., and H.J.M. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the Korea Institute of Planning and Evaluation for Technology in Food, Agriculture and Forestry (IPET) through the Agricultural Machinery/Equipment Localization Technology Development Program, the Ministry of Agriculture, Food and Rural Affairs (MAFRA-321057052HD030 to C.W.L.). Lutfun Nahar gratefully acknowledges the financial support of the European Regional Development Fund - Project ENOCH (No. CZ.02.1.01/0.0/0.0/16_019/0000868) and the Czech Agency Grant - Project 23-05474S.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflict of interest.

References

- [1] R.A. Halberstein, Medicinal plants: historical and cross-cultural usage patterns, *Annals of epidemiology* 15(9) (2005) 686-699.
- [2] L. Katz, R.H. Baltz, Natural product discovery: past, present, and future, *Journal of Industrial Microbiology and Biotechnology* 43(2-3) (2016) 155-176.
- [3] J. Tamokou, A. Mbaveng, V. Kuete, Antimicrobial activities of African medicinal spices and vegetables, *Medicinal spices and vegetables from Africa*, Elsevier 2017, pp. 207-237.
- [4] D.J. Mabberley, *The plant-book: a portable dictionary of the vascular plants*, Cambridge university press 1997.
- [5] A.-C. Scheen, V.A. Albert, Nomenclatural and taxonomic changes within the Leucas clade (Lamioideae; Lamiaceae), *Systematics and Geography of Plants* (2007) 229-238.
- [6] F. Ghahremaninejad, E. Hoseini, *Identification of Medicinal and Aromatic Plants of Iran*, Valiollah Mozaffarian. Farhang Moaser Publishers, Tehran (2012). 1444 pp., 2470 colored images (Language: Mainly Persian with English preface and several indexes). Hardback, ISBN: 978-600-1050-31-2. Format: 23.5× 15.5 cm. Price: 900000 IR-Rials, Elsevier, 2015.
- [7] K. Javidnia, R. Miri, M. Soltani, A. Khosravi, Chemical constituents of the essential oil of *Otostegia michauxii* Briq. from Iran, *Journal of Essential Oil Research* 22(1) (2010) 1-2.

- 1137 [8] K. Rechinger, *Otostegia persica* (Labiatae), *Flora Iranica*. Graz: Akademische Druck-u
1138 (1982).
- 1139 [9] V. Mozafarrian, *Dictionary of the names of Iranian plants*, Iran, Tehran, Farhange moaser
1140 (1998).
- 1141 [10] A. Zargari, *Medicinal plants*. 2nd edition, Tehran University Publisher, (Persian), Tehran,
1142 1989.
- 1143 [11] A. Karami, H. Esmaeili, D. Shahbazian, Essential oil composition of *Rydingia michauxii* (Briq.)
1144 Scheen & VA Albert endemic of Iran, *Natural product research* 32(2) (2018) 229-233.
- 1145 [12] S. Rosselli, G. Fontana, M. Bruno, A review of the phytochemistry, traditional uses, and
1146 biological activities of the Genus *Ballota* and *Otostegia*, *Planta medica* 85(11/12) (2019) 869-910.
- 1147 [13] Z. Sadeghi, M. Akaberi, J. Valizadeh, *Otostegia persica* (Lamiaceae): A review on its
1148 ethnopharmacology, phytochemistry, and pharmacology, *Avicenna journal of phytomedicine* 4(2)
1149 (2014) 79.
- 1150 [14] S. Sut, A. Tahmasebi, N. Ferri, I. Ferrarese, I. Rossi, G. Panighel, M.G. Lupo, F. Maggi, A.
1151 Karami, S. Dall'Acqua, NMR, LC-MS Characterization of *Rydingia michauxii* Extracts,
1152 Identification of Natural Products Acting as Modulators of LDLR and PCSK9, *Molecules* 27(7)
1153 (2022) 2256.
- 1154 [15] K. Rechinger, *Flora Iranica*. Graz-Austria: Academic Druck-u, Verlagsanstalt 150 (1982) 292-
1155 313.
- 1156 [16] A. Ghahraman, *Color atlas of Iranian flora*, Research Institute of Forests and Rangelands
1157 Publishing, Tehran 9 (1996) 3071.
- 1158 [17] Z. Jamzad, *Flora of Lamiaceae family*. Research Institute of Forests and Rangelands,
1159 Tehran, Iran, 1066p, 2013.
- 1160 [18] S. Khan, F. Syed, Bioactive constituents from genus *Otostegia*, *SARJ of Physical Sci* 1 (2013)
1161 15-25.
- 1162 [19] O. Safa, M.A. Soltanipoor, S. Rastegar, M. Kazemi, K.N. Dehkordi, A. Ghannadi, An
1163 ethnobotanical survey on hormozgan province, Iran, *Avicenna journal of phytomedicine* 3(1)
1164 (2013) 64.
- 1165 [20] M.A. Toori, B. Joodi, H. Sadeghi, H. Sadeghi, M. Jafari, M.S. Talebianpoor, F. Mehraban, M.
1166 Mostafazadeh, M. Ghavamizadeh, Hepatoprotective activity of aerial parts of *Otostegia persica*
1167 against carbon tetrachloride-induced liver damage in rats, *Avicenna journal of phytomedicine* 5(3)
1168 (2015) 238.
- 1169 [21] Z. Tofighi, S. Ostad, S. Khezrrahdoost, H. Salehizadeh, N. Yassa, Potent anti-nociceptive
1170 and anti-inflammatory effects of methanol fraction of *Otostegia persica* extract and its
1171 components, *Research Journal of Pharmacognosy* 4(2) (2017) 23-29.
- 1172 [22] A. Ganjali, A. Sotoudeh, A. Jahanshahi, M.A. Takhtfooladi, A. Bazzazan, N. Roodbari, M.P.
1173 Harati, *Otostegia persica* extraction on healing process of burn wounds, *Acta Cirurgica Brasileira*
1174 28 (2013) 407-411.
- 1175 [23] L. Safaeian, N. Ghasemi-Dehkordi, S.H. Javanmard, H. Namvar, Antihypertensive and
1176 antioxidant effects of a hydroalcoholic extract obtained from aerial parts of *Otostegia persica*
1177 (Burm.) Boiss, *Research in Pharmaceutical Sciences* 10(3) (2015) 192.
- 1178 [24] S.A.M. Ayatollahi, F. Kobarfard, J. Asgarpanah, M.I. Choudhary, Antiglycation activity of
1179 *Otostegia persica* (Burm.) Boiss, *African Journal of Biotechnology* 9(24) (2010) 3645-3648.
- 1180 [25] A.K. Aria, M.A. Soltanipoor, R. Asadpour, Study of some Ecological Characteristics and
1181 Potential Allelopathic of *Otostegia persica* in Hormozgan Province, *Journal of Medicinal plants*
1182 and By-product 5(2) (2016) 211-215.
- 1183 [26] S. Esmaeili, F. Naghibi, M. Mosaddegh, Indigenous knowledge of traditionally used plants
1184 from Iran for fever/malaria treatment, *Planta Medica* 76(12) (2010) P509.

1185 [27] M. Irani, S. Esmaeili, A. Pirani, F. Naghibi, M. Mosaddegh, Evaluation of antiplasmodial
1186 activity of some plants ethnopharmacologically used to treat malaria in Iran, The International
1187 Congress on Complementary and Alternative Medicine (2015).
1188 [28] S.H. Hosseini, H. Bibak, A.R. Ghara, A. Sahebkar, A. Shakeri, Ethnobotany of the medicinal
1189 plants used by the ethnic communities of Kerman province, Southeast Iran, Journal of
1190 Ethnobiology and Ethnomedicine 17(1) (2021) 1-35.
1191 [29] Z. Sadeghi, K. Kuhestani, V. Abdollahi, A. Mahmood, Ethnopharmacological studies of
1192 indigenous medicinal plants of Saravan region, Baluchistan, Iran, Journal of Ethnopharmacology
1193 153(1) (2014) 111-118.
1194 [30] N. Ghasemi-Dehkordi, K. Sartavi, E. Yadegari, Collecting and examining the traditional uses
1195 of selected plants of Jam and Riz, Journal of Islamic and Iranian Traditional Medicine 4(2) (2013)
1196 199-208.
1197 [31] F. Mohammadi, Ahmadi, Abas, Mokhtarpour, Mehdi, Quantitative evaluation of biodiversity of
1198 medicinal plants and their use in
1199 Darab city, Iranian Journal of Anthropology 18(33) (2022).
1200 [32] A. Zargari, Medicinal plants, Vol 1; Tehran, Tehran university press, 1990.
1201 [33] A. Tahmasebi, S.M. Hosseini, A. Karami, A. Afsharifar, A.R. Sharifi Olounabadi, Variation in
1202 essential oil composition of *Rydingia michauxii* at the three developmental stages, Natural product
1203 research 35(2) (2021) 342-345.
1204 [34] Z. Tofighi, F. Alipour, N. Yassa, A. Hadjiakhoondi, H. Hadavinia, S. Goodarzy, R. Golestani,
1205 Chemical composition and antioxidant activity of *Otostegia persica* essential oil from Iran, Int J
1206 Essen Oil Ther 3 (2009) 45-48.
1207 [35] K. Javidnia, R. Miri, M. Soltani, A. Khosravi, Essential oil composition of *Otostegia persica*
1208 Boiss. from Iran, Journal of Essential Oil Research 22(6) (2010) 609-610.
1209 [36] F. Shariffar, V. Mozaffarian, S. Moradkhani, Comparison of antioxidant and free radical
1210 scavenging activities of the essential oils from flowers and fruits of *Otostegia persica* Boiss,
1211 Pakistan Journal of Biological Sciences: PJBS 10(21) (2007) 3895-3899.
1212 [37] M. Nematinejad, A.S. Raisi, M.R. Asgharipour, F. Nosrati, Study of edaphic, morphological
1213 and phytochemical components of wild
1214 population of *Otostegia persica* B. in habitats of Baluchistan, Iran, Journal of Horticultural Science
1215 36 (2022) 429-442.
1216 [38] H. Bhardawaj, N. Vasudeva, S. Sharma, Phytochemistry and Pharmacological Aspects of
1217 Apigenin: A Review, Natural Products Journal 13(4) (2023) 64-82.
1218 [39] A.K. Singh, R.K. Singla, A.K. Pandey, Chlorogenic Acid: A Dietary Phenolic Acid with
1219 Promising Pharma-cotherapeutic Potential, Current Medicinal Chemistry 30(34) (2023) 3905-
1220 3926.
1221 [40] W. He, T. Fang, P. Tu, Research progress on pharmacological activities of echinacoside,
1222 Zhongguo Zhongyao Zazhi 34(4) (2009) 476-479.
1223 [41] J. Liu, L. Yang, Y. Dong, B. Zhang, X. Ma, Echinacoside, an Inestimable Natural Product in
1224 Treatment of Neurological and other Disorders, Molecules 23(5) (2018).
1225 [42] M. Sova, L. Saso, Natural sources, pharmacokinetics, biological activities and health benefits
1226 of hydroxycinnamic acids and their metabolites, Nutrients 12(8) (2020) 1-30.
1227 [43] M. Shahbaz, M. Imran, S.A. Alsagaby, H. Naeem, W. Al Abdulmonem, M. Hussain, M.A.
1228 Abdelgawad, A.H. El-Ghorab, M.M. Ghoneim, M. El-Sherbiny, A.V. Atoki, C.G. Awuchi,
1229 Anticancer, antioxidant, ameliorative and therapeutic properties of kaempferol, International
1230 Journal of Food Properties 26(1) (2023) 1140-1166.
1231 [44] M. Çetinkaya, Y. Baran, Therapeutic Potential of Luteolin on Cancer, Vaccines 11(3) (2023).
1232 [45] S. Punia Bangar, P. Kajla, V. Chaudhary, N. Sharma, F. Ozogul, Luteolin: A flavone with
1233 myriads of bioactivities and food applications, Food Bioscience 52 (2023).

1234 [46] K. Alipieva, L. Korkina, I.E. Orhan, M.I. Georgiev, Verbascoside - A review of its occurrence,
 1235 (bio)synthesis and pharmacological significance, *Biotechnology Advances* 32(6) (2014) 1065-
 1236 1076.

1237 [47] W.G. Wang, P. Wang, Z.Q. Yang, M.X. Li, X.Y. Tian, Pharmacological effects of
 1238 verbascoside: research advances, *Journal of International Pharmaceutical Research* 47(12)
 1239 (2020) 1078-1087.

1240 [48] S. Ayatollahi, F. Kobarfard, J. Asgarpanah, Z. Ahmed, Chemical constituents from *Otostegia*
 1241 *persica*, *Journal of the Chemical Society of Pakistan* 29(1) (2007) 61-63.

1242 [49] S. Ayatollahi, F. Kobarfard, J. Asgarpanah, R. RAHMATI, G. Fanai, C. Iqbal, Diterpenoids of
 1243 *Otostegia persica* (Burm.) Boiss, (2009).

1244 [50] N. Yassa, F. Sharififar, A. Shafiee, *Otostegia persica*. as a Source of Natural Antioxidants,
 1245 *Pharmaceutical biology* 43(1) (2005) 33-38.

1246 [51] M. Doorandishan, S. Pirhadi, M. Gholami, A.R. Jassbi, In Silico Studies of Furano-Labdane
 1247 Diterpenoids from *Rydingia Persica* Scheen (*Otostegia Persica*) as α -Glucosidase Enzyme
 1248 Inhibitor, Available at SSRN 4391586 (2023).

1249 [52] H.M. Gholami, E., F. Sargezy, A. Ainali, Phytosynthesis of silver nanoparticles using
 1250 *Otostegia persica*, *Ecophysiology & Phytochemistry of Medicinal and Aromatic Plants* 9(2) (2023)
 1251 65-77.

1252 [53] Z. Tofighi, F. Alipour, H. Hadavinia, M. Abdollahi, A. Hadjiakhoondi, N. Yassa, Effective
 1253 antidiabetic and antioxidant fractions of *Otostegia persica* extract and their constituents,
 1254 *Pharmaceutical biology* 52(8) (2014) 961-966.

1255 [54] A. Manzari-Tavakoli, I. Pouraboli, M.-M. Yaghoobi, M. Mehrabani, S.-M. Mirtadzadini,
 1256 Antihyperglycemic, antilipid peroxidation, and insulin secretory activities of *Otostegia persica*
 1257 shoot extract in streptozotocin-induced diabetic rats and in vitro C187 pancreatic β -cells,
 1258 *Pharmaceutical Biology* 51(2) (2013) 253-259.

1259 [55] A. Parvin, P. Yaghmaei, M. Nouredini, S.A. Haeri Roohani, S. Aminzadeh, Comparative
 1260 effects of quercetin and hydroalcoholic extract of *Otostegia persica* boiss with atorvastatin on
 1261 atherosclerosis complication in male wistar rats, *Food Science & Nutrition* 7(9) (2019) 2875-2887.

1262 [56] F. Ansari, H. Shafaroodi, J. Asgarpanah, Anticonvulsant Activity of *Otostegia persica* (Burm.)
 1263 Boiss, *Biosci. Biotechnol. Res. Asia* 11 (2014) 733-737.

1264 [57] S. Akbarzadeh, P. Bazzi, A. Daneshi, I. Nabipour, K. Pourkhalili, G. Mohebbi, K. Sartavi, M.
 1265 Abdi, M. Mirzaei, A. Bargahi, Anti-diabetic effect of *Otostegia persica* extract on diabetic rats, *J*
 1266 *Med Plants Res* 6(16) (2012) 3176-80.

1267 [58] M. Doorandishan, M. Hossieni, M. Malekaneh, G. Bagherzade, Effect of *Otostegia persica*'s
 1268 root extract on the blood biochemical factors in diabetic hyperlipidemic rats, *Internal Medicine*
 1269 *Today* 20(1) (2014) 17-21.

1270 [59] M.R. Ebrahimipoor, Z. Khaksar, A. Noorafshan, Anti-diabetic effect of orally administered
 1271 *Otostegia persica* extract on streptozotocin diabetic rats, *Comparative Clinical Pathology* 20
 1272 (2011) 523-525.

1273 [60] M. Rezaian, T. Shomali, A. Dilmaghanian, A. Rassouli, Ethanolic extract of *Otostegia persica*
 1274 ameliorates bone loss in diabetic rats irrespective to its glucose lowering effect, *Comparative*
 1275 *Clinical Pathology* 23 (2014) 1147-1151.

1276 [61] M.R. Ebrahimipoor-Mashhadi, Z. Khaksar, A. Noorafshan, B. Mogheisi, Stereological study
 1277 of the effects of orally administrated *Otostegia persica* extract on pancreatic beta cells in male
 1278 diabetic rats, *Comparative Clinical Pathology* 23 (2014) 761-767.

1279 [62] M. Hedayati, I. Pouraboli, The effect of methanolic extract of *Otostegia persica* on serum
 1280 glucose level and renal function indicators in streptozotocin induced diabetic rats, *Zahedan*
 1281 *Journal of Research in Medical Sciences* 14(5) (2012).

1282 [63] M. Hedayati, I. Pouraboli, M. Mirtajaddini, The effect of methanolic extract of *Otostegia*
1283 *persica* on serum levels of glucose and liver function enzymes in streptozotocin-induced diabetic
1284 male rats, *Journal of Rafsanjan University of Medical Sciences* 10(2) (2011) 84-93.

1285 [64] M. Hedayati, I. Pouraboli, B. Pouraboli, Effect of methanolic extract of *Otostegia persica* on
1286 serum levels of glucose and lipids in type I diabetic male rats, *Iranian Journal of Endocrinology*
1287 *and Metabolism* 12(4) (2010).

1288 [65] M. Hedayati, I. Pouraboli, B. Pouraboli, S. Dabiri, A. Javadi, Effects of *Otostegia persica*
1289 extract on serum level of glucose and morphology of pancreas in diabetic rats, *Koomesh* 13(2)
1290 (2012).

1291 [66] F. Ostovan, A. Gol, A. Javadi, Protective properties of *Rydingia persica* in reproductive
1292 complications induced by diabetes in male rats: An experimental study, *International Journal of*
1293 *Reproductive BioMedicine* 20(2) (2022) 123.

1294 [67] M. Sharifi-Rad, P. Pohl, F. Epifano, Phytofabrication of silver nanoparticles (AgNps) with
1295 pharmaceutical capabilities using *otostegia persica* (burm.) boiss. leaf extract, *Nanomaterials*
1296 11(4) (2021) 1045.

1297 [68] M.A. Takhtfooladi, H.A. Takhtfooladi, F. Moayer, P. Karimi, H.A. Asl, Effect of *Otostegia*
1298 *persica* extraction on renal injury induced by hindlimb ischemia-reperfusion: a rat model,
1299 *International Journal of Surgery* 13 (2015) 124-130.

1300 [69] M. Nateghpour, A. Miahpour, G.H. Edirssian, E. Sori, A. Motevalli, Effectiveness of ethanolic
1301 extract of *Otostegia Persica* against *Plasmodium Berghei* in comparison with chloriquine in white
1302 mice using in vivo tests, *Journal of School of Public Health & Institute of Public Health Research*
1303 6(1) (2008).

1304 [70] M. Nateghpour, L. Farivar, E. Souiri, H. Hajjaran, M. Mohebbali, A.M. Haghi, The effect of
1305 *Otostegia persica* in combination with chloroquine on chloroquine-sensitive and chloroquine-
1306 resistant strains of *Plasmodium berghei* using in-vivo fixed ratios method, *Iranian Journal of*
1307 *Pharmaceutical Research: IJPR* 11(2) (2012) 583.

1308 [71] G. Asghari, H. Nourallah, S. Havaie, L. Issa, Antimicrobial activity of *Otostegia persica* Boiss.
1309 extracts, *Research in pharmaceutical sciences* 1(1) (2007) 53-58.

1310 [72] K. Javidnia, R. Miri, M. Assadollahi, M. Gholami, M. Ghaderi, Screening of selected plants
1311 growing in Iran for antimicrobial activity, *Iranian Journal of Science & Technology, Transaction A*
1312 33 (2009) 329-333.

1313 [73] O. Firuzi, K. Javidnia, M. Gholami, M. Soltani, R. Miri, Antioxidant activity and total phenolic
1314 content of 24 Lamiaceae species growing in Iran, *Natural product communications* 5(2) (2010)
1315 1934578X1000500219.

1316 [74] Z. Tofighi, F. Alipour, S. Goodarzi, N. Yassa, A. Hadjiakhoondi, H. Hadavinia, Phytochemical
1317 and antidiabetic investigations of *Otostegia persica* from Iran, *Planta Medica* 75(09) (2009) PH26.

1318 [75] F.G. Rahdari, K. Shahanipour, R. Monajemi, M. Adibnejad, Comparison of the antisclerotic
1319 effect of hydroalcoholic extracts of *Ocimum basilicum* and *Otostegia persica* with quinacrine by
1320 inhibition of phospholipase A2 in male Wistar rats, *Avicenna Journal of Phytomedicine* 12(2)
1321 (2022) 175.

1322 [76] M. Rezaeian, A. Dilmaghanian, T. Shomali, M. Adibmoradi, A. Rasooli, Bone protective
1323 effects following ethanolic extract (*Otostegia persica*) administration in streptozotocin-induced
1324 diabetic rats: histomorphometric study, *Journal of Veterinary Research* 70(1) (2015).

1325 [77] A. Dehghani Nazhvani, M. Razmkhah, A. Jassbi, M. Khademalizadeh, A. Mahmoodi,
1326 Evaluation of anticancer effect of *Hibiscus Sabdarifa*, *Otostegia Persica* *Otostegia Aucheri*, and
1327 *Otostegia Michauxii* on oral squamous cell carcinoma cell line, *Journal of Dental Medicine* 32(4)
1328 (2020) 208-215.

1329 [78] A. Tahmasebi, A. Karami, S.M. Hosseini, A. Afsharifar, A. Moghadam, Y. Biniiaz, Cytotoxic
1330 and antimicrobial activities of *Rydingia michauxii* methanolic extracts during various growth
1331 stages, *Cleaner Engineering and Technology* 4 (2021) 100225.

1332 [79] L. Safaeian, S. Yaghoobi, S. Javanmard, N. Ghasemi-Dehkordi, The effect of hydroalcoholic
 1333 extract of *Otostegia persica* (Burm.) Boiss. against H₂O₂-induced oxidative stress in human
 1334 endothelial cells, *Research Journal of Pharmacognosy* (RJP) 4(1) (2017) 51-58.
 1335 [80] S. Esmaeili, M. Hamzeloo-Moghadam, S. Ghaffari, M. Mosaddegh, Cytotoxic activity
 1336 screening of some medicinal plants from south of Iran, *Research Journal of Pharmacognosy* 1(4)
 1337 (2014) 19-25.
 1338 [81] S.N. Bezenjani, I. Pouraboli, R.M. Afshar, G. Mohammadi, Hepatoprotective effect of
 1339 *Otostegia persica* Boiss. shoot extract on carbon tetrachloride-induced acute liver damage in rats,
 1340 *Iranian Journal of Pharmaceutical Research: IJPR* 11(4) (2012) 1235.
 1341 [82] V. Hajhashemi, M. RABANI, G.R. ASGHARI, S.Z. KARAMI, Effects of *Otostegia persica*
 1342 (Burm.) Boiss on morphine withdrawal syndrome in mice, (2004).
 1343 [83] H. Sadeghi, M. Soltani, E.P. Kokhdan, R. Abbasi, H. Sadeghi, M. Mostafazade, F. Mehraban,
 1344 Renoprotective effect of *Otostegia persica* on vancomycin-induced nephrotoxicity in rats,
 1345 *Comparative Clinical Pathology* 30 (2021) 431-439.
 1346 [84] F. Shrififar, N. Yasa, A. Shafiei, Antioxidant activity of *Otostegia persica* (Labiatae) and its
 1347 constituents, (2003).
 1348 [85] A. Rakhshani, E. Alizadeh, E. Ahmadifar, M. Shahriari Moghadam, Effect of dietary gold
 1349 powder (*Otostegia persica*) on blood parameters, antioxidant defense and immune of common
 1350 carp (*Cyprinus carpio*), *Journal of Aquatic Physiology and Biotechnology* 9(1) (2021) 39-56.
 1351 [86] B.A. Bohm, Introduction to flavonoids, Harwood academic publishers 1998.
 1352 [87] G. Scott, Antioxidants in science, technology, medicine and nutrition, Elsevier 1997.
 1353 [88] E. Elstner, E. Kleber, Radical scavenger properties of leucocyanidine, Proc 3 rd Int
 1354 Symposium on Flavonoids in Biology & Medicine, Singapore, 1990, pp. 221-235.
 1355 [89] M. Hertog, P.C. Hollman, Potential health effects of the dietary flavonol quercetin, *European*
 1356 *Journal of Clinical Nutrition* 50(2) (1996) 63-71.
 1357 [90] J. Robak, R.J. Gryglewski, Flavonoids are scavengers of superoxide anions, *Biochemical*
 1358 *pharmacology* 37(5) (1988) 837-841.
 1359 [91] Y.M.C. Zhang, Protective effect of quercetin on Aroclor 1254-induced oxidative damage in
 1360 cultured chicken spermatogonial cells, *Toxicological Sciences* 88(2) (2005) 545-550.
 1361 [92] J.Y. Park, K.A. Kang, K.C. Kim, J.W. Cha, E.H. Kim, J.W. Hyun, Morin induces heme
 1362 oxygenase-1 via ERK-Nrf2 signaling pathway, *Journal of cancer prevention* 18(3) (2013) 249.
 1363 [93] Y.-M. Jeong, Y.-G. Choi, D.-S. Kim, S.-H. Park, J.-A. Yoon, S.-B. Kwon, E.-S. Park, K.-C.
 1364 Park, Cytoprotective effect of green tea extract and quercetin against hydrogen peroxide-induced
 1365 oxidative stress, *Archives of pharmacal research* 28 (2005) 1251-1256.
 1366 [94] J. Zhang, L.D. Melton, A. Adaim, M.A. Skinner, Cytoprotective effects of polyphenolics on H
 1367 ₂ O ₂-induced cell death in SH-SY5Y cells in relation to their antioxidant activities, *European Food*
 1368 *Research and Technology* 228 (2008) 123-131.
 1369 [95] H.-B. Xiao, X.-Y. Lu, X.-j. Chen, Z.-L. Sun, Protective effects of kaempferol against
 1370 endothelial damage by an improvement in nitric oxide production and a decrease in asymmetric
 1371 dimethylarginine level, *European journal of pharmacology* 616(1-3) (2009) 213-222.
 1372 [96] M. Nardini, P. Pisu, V. Gentili, F. Natella, M. Di, F. Piccolella, C. Scaccini, Effect of caffeic
 1373 acid on tert-butyl hydroperoxide-induced oxidative stress in U937, *Free Radical Biology and*
 1374 *Medicine* 25(9) (1998) 1098-1105.
 1375 [97] U. Kang, J. Park, A.-R. Han, M.H. Woo, J.-H. Lee, S.K. Lee, T.-S. Chang, H.A. Woo, E.K.
 1376 Seo, Identification of cytoprotective constituents of the flower buds of *Tussilago farfara* against
 1377 glucose oxidase-induced oxidative stress in mouse fibroblast NIH3T3 cells and human
 1378 keratinocyte HaCaT cells, *Archives of pharmacal research* 39 (2016) 474-480.
 1379 [98] C.-M. Lin, C.-T. Chen, H.-H. Lee, J.-K. Lin, Prevention of cellular ROS damage by isovitexin
 1380 and related flavonoids, *Planta medica* 68(04) (2002) 365-367.

1381 [99] M.-D. Chen, P.-Y. Lin, C.-T. Tsou, J.-J. Wang, W.-H. Lin, Selected metals status in patients
1382 with noninsulin-dependent diabetes mellitus, *Biological trace element research* 50 (1995) 119-
1383 124.

1384 [100] V.R. Osório e Castro, Chromium in a series of Portuguese plants used in the herbal
1385 treatment of diabetes, *Biological trace element research* 62 (1998) 101-106.

1386 [101] P.K. Mukherjee, K. Maiti, K. Mukherjee, P.J. Houghton, Leads from Indian medicinal plants
1387 with hypoglycemic potentials, *Journal of ethnopharmacology* 106(1) (2006) 1-28.

1388 [102] M. Cnop, N. Welsh, J.-C. Jonas, A. Jorns, S. Lenzen, D.L. Eizirik, Mechanisms of pancreatic
1389 β -cell death in type 1 and type 2 diabetes: many differences, few similarities, *Diabetes*
1390 54(suppl_2) (2005) S97-S107.

1391 [103] S. Kannappan, C. Anuradha, Insulin sensitizing actions of fenugreek seed polyphenols,
1392 quercetin & metformin in a rat model, *Indian journal of medical research* 129(4) (2009) 401-408.

1393 [104] M. Bnouham, A. Ziyat, H. Mekhfi, A. Tahri, A. Legssyer, Medicinal plants with potential
1394 antidiabetic activity-A review of ten years of herbal medicine research (1990-2000), *Dubai*
1395 *Diabetes and Endocrinology Journal* 14(1) (2006) 1-25.

1396 [105] A.E. Abd El-Baky, Quercetin protective action on oxidative stress, sorbitol, insulin resistance
1397 and β -cells function in experimental diabetic rats, *Int. J. Pharm. Stud. Res* 2(2) (2011) 11-8.

1398 [106] M. Lamela, I. Cadavid, A. Gato, J. Calleja, Effects of *Lythrum salicaria* in normoglycemic
1399 rats, *Journal of Ethnopharmacology* 14(1) (1985) 83-91.

1400 [107] E.B. de Melo, A. da Silveira Gomes, I. Carvalho, α - and β -Glucosidase inhibitors: chemical
1401 structure and biological activity, *Tetrahedron* 62(44) (2006) 10277-10302.

1402 [108] A. Gholamhoseinian, H. FALAH, F. SHARIFIFAR, A.S. MIRTAJ, The inhibitory effect of
1403 some Iranian plants extracts on the alpha glucosidase, (2008).

1404 [109] S. Rouzbehan, S. Moein, A. Homaei, M.R. Moein, Kinetics of α -glucosidase inhibition by
1405 different fractions of three species of Labiatae extracts: a new diabetes treatment model,
1406 *Pharmaceutical Biology* 55(1) (2017) 1483-1488.

1407 [110] N. Kamalakkannan, P.S.M. Prince, Antihyperglycaemic and antioxidant effect of rutin, a
1408 polyphenolic flavonoid, in streptozotocin-induced diabetic wistar rats, *Basic & clinical*
1409 *pharmacology & toxicology* 98(1) (2006) 97-103.

1410 [111] R.J. Marles, N.R. Farnsworth, Antidiabetic plants and their active constituents,
1411 *Phytomedicine* 2(2) (1995) 137-189.

1412 [112] O. Coskun, M. Kanter, A. Korkmaz, S. Oter, Quercetin, a flavonoid antioxidant, prevents
1413 and protects streptozotocin-induced oxidative stress and β -cell damage in rat pancreas,
1414 *Pharmacological research* 51(2) (2005) 117-123.

1415 [113] A. Kato, Y. Minoshima, J. Yamamoto, I. Adachi, A.A. Watson, R.J. Nash, Protective effects
1416 of dietary chamomile tea on diabetic complications, *Journal of agricultural and food chemistry*
1417 56(17) (2008) 8206-8211.

1418 [114] W.C. Cho, W.-S. Chung, S.K. Lee, A.W. Leung, C.H. Cheng, K.K. Yue, Ginsenoside Re of
1419 *Panax ginseng* possesses significant antioxidant and antihyperlipidemic efficacies in
1420 streptozotocin-induced diabetic rats, *European journal of pharmacology* 550(1-3) (2006) 173-179.

1421 [115] Z. Yu, W.P. Fong, C.H. Cheng, The Dual Actions of Morin as a Hypouricemic Agent:
1422 Uricosuric Effect and Xanthine Oxidase Inhibitory Activity, *Journal of Pharmacology and*
1423 *Experimental Therapeutics* (2005).

1424 [116] A. Khaki, A. KHAKI, M. Nouri, A.H.R. AHMADI, H. Rastgar, S. Rezazadeh, A.F. FATHI, M.
1425 Ghanbari, Evaluation effects of Quercetin on liver apoptosis in streptozotocin-induced diabetic rat,
1426 (2009).

1427 [117] P. McCue, D. Vatter, K. Shetty, Inhibitory effect of clonal oregano extracts against porcine
1428 pancreatic amylase in vitro, *Asia Pacific Journal of Clinical Nutrition* 13(4) (2004) 401-408.

1429 [118] A.S. Dias, M. Porawski, M. Alonso, N. Marroni, P.S. Collado, J. Gonzalez-Gallego,
 1430 Quercetin decreases oxidative stress, NF- κ B activation, and iNOS overexpression in liver of
 1431 streptozotocin-induced diabetic rats, *The Journal of nutrition* 135(10) (2005) 2299-2304.
 1432 [119] B. Chakravarthy, G. Saroj, S. Gambhir, K. Gode, Pancreatic beta cell regeneration—a novel
 1433 antidiabetic mechanism of *Pterocarpus marsupium* roxb, *Indian journal of pharmacology* 12(2)
 1434 (1980) 123.
 1435 [120] M. Manickam, M. Ramanathan, M. Farboodniay Jahromi, J. Chansouria, A. Ray,
 1436 Antihyperglycemic activity of phenolics from *Pterocarpus marsupium*, *Journal of natural products*
 1437 60(6) (1997) 609-610.
 1438 [121] D.F. Pereira, L.H. Cazarolli, C. Lavado, V. Mengatto, M.S.R.B. Figueiredo, A. Guedes, M.G.
 1439 Pizzolatti, F.R.M.B. Silva, Effects of flavonoids on α -glucosidase activity: potential targets for
 1440 glucose homeostasis, *Nutrition* 27(11-12) (2011) 1161-1167.
 1441 [122] F. Sharifar, N. Yasa, A. Shafiei, Antioxidant activity of *Otostegia persica* (Labiatae) and its
 1442 constituents, *Iranian Journal of Pharmaceutical Research*
 1443 (2003) 235-239.
 1444 [123] O. Kwon, P. Eck, S. Chen, C.P. Corpe, J.H. Lee, M. Kruhlak, M. Levine, Inhibition of the
 1445 intestinal glucose transporter GLUT2 by flavonoids, *The FASEB Journal* 21(2) (2007) 366-377.
 1446 [124] E. Youl, G. Bardy, R. Magous, G. Cros, F. Sejalon, A. Virsolvy, S. Richard, J. Quignard, R.
 1447 Gross, P. Petit, Quercetin potentiates insulin secretion and protects INS-1 pancreatic β -cells
 1448 against oxidative damage via the ERK1/2 pathway, *British journal of pharmacology* 161(4) (2010)
 1449 799-814.
 1450 [125] M. Vessal, M. Hemmati, M. Vasei, Antidiabetic effects of quercetin in streptozocin-induced
 1451 diabetic rats, *Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology*
 1452 135(3) (2003) 357-364.
 1453 [126] S. Subash, P. Subramanian, Effect of morin on the levels of circulatory liver markers and
 1454 redox status in experimental chronic hyperammonaemic rats, *Singapore medical journal* 49(8)
 1455 (2008) 650.
 1456 [127] P. Paoli, P. Cirri, A. Caselli, F. Ranaldi, G. Bruschi, A. Santi, G. Camici, The insulin-mimetic
 1457 effect of Morin: A promising molecule in diabetes treatment, *Biochimica et Biophysica Acta (BBA)-*
 1458 *General Subjects* 1830(4) (2013) 3102-3111.
 1459 [128] M.S. Ola, A.M. Aleisa, S.S. Al-Rejaie, H.M. Abuohashish, M.Y. Parmar, A.S. Alhomida, M.M.
 1460 Ahmed, Flavonoid, morin inhibits oxidative stress, inflammation and enhances neurotrophic
 1461 support in the brain of streptozotocin-induced diabetic rats, *Neurological sciences* 35 (2014) 1003-
 1462 1008.
 1463 [129] W.K. Oh, C.H. Lee, M.S. Lee, E.Y. Bae, C.B. Sohn, H. Oh, B.Y. Kim, J.S. Ahn, Antidiabetic
 1464 effects of extracts from *Psidium guajava*, *Journal of ethnopharmacology* 96(3) (2005) 411-415.
 1465 [130] S.K. Basha, V.S. Kumari, In vitro antidiabetic activity of *Psidium guajava* leaves extracts,
 1466 *Asian Pacific Journal of Tropical Disease* 2 (2012) S98-S100.
 1467 [131] R. Vinayagam, B. Xu, Antidiabetic properties of dietary flavonoids: a cellular mechanism
 1468 review, *Nutrition & metabolism* 12 (2015) 1-20.
 1469 [132] A.P. Rauter, A. Martins, C. Borges, H. Mota-Filipe, R. Pinto, B. Sepodes, J. Justino,
 1470 Antihyperglycaemic and protective effects of flavonoids on streptozotocin-induced diabetic rats,
 1471 *Phytotherapy Research* 24(S2) (2010) S133-S138.
 1472 [133] K. Chayarop, R. Temsiririrkkul, P. Peungvicha, Y. Wongkrajang, W. Chuakul, S. Amnuoyopol,
 1473 N. Ruangwises, Antidiabetic effects and in vitro antioxidant activity of *Pseuderanthemum*
 1474 *palatiferum* (Nees) Radlk. ex Lindau leaf aqueous extract, *Pharm. Soc. Asia* 38 (2011) 13-22.
 1475 [134] H. Bischoff, The mechanism of alpha-glucosidase inhibition in the management of diabetes,
 1476 *Clinical and investigative medicine. Medecine clinique et experimentale* 18(4) (1995) 303-311.

1477 [135] S. Moein, E. Pimoradloo, M. Moein, M. Vessal, Evaluation of antioxidant potentials and α -
 1478 amylase inhibition of different fractions of labiatae plants extracts: as a model of antidiabetic
 1479 compounds properties, *BioMed research international* 2017 (2017).
 1480 [136] S. Moein, S. Jahanshai, M. Rahimzadeh, M. Moein, Kinetic of α -amylase and comparison
 1481 its inhibition by ethanol and aqueous extracts of *Otostegia persica*, *Salvia mirzayanii* and *Zataria*
 1482 *multiflora*, *Iranian Journal of Science and Technology, Transactions A: Science* 42 (2018) 339-
 1483 345.
 1484 [137] M. Kurahashi, K. Inomata, Amylase secretion by parotid glands and pancreas of diabetic
 1485 rats during feeding, *American Journal of Physiology-Gastrointestinal and Liver Physiology* 254(6)
 1486 (1988) G878-G882.
 1487 [138] F.A. Van de Laar, Alpha-glucosidase inhibitors in the early treatment of type 2 diabetes,
 1488 *Vascular health and risk management* 4(6) (2008) 1189-1195.
 1489 [139] Y. Tatami, S. Suzuki, H. Ishii, Y. Shibata, N. Osugi, T. Ota, Y. Kawamura, A. Tanaka, K.
 1490 Takeshita, T. Murohara, Impact of serum bilirubin levels on carotid atherosclerosis in patients with
 1491 coronary artery disease, *IJC Metabolic & Endocrine* 5 (2014) 24-27.
 1492 [140] O. Azizova, A. Aseichev, A. Piryazev, E. Roitman, O. Shcheglovitova, Effects of oxidized
 1493 fibrinogen on the functions of blood cells, blood clotting, and rheology, *Bulletin of experimental*
 1494 *biology and medicine* 144 (2007) 397-407.
 1495 [141] L.G. Costa, J.M. Garrick, P.J. Roqu  , C. Pellacani, Mechanisms of neuroprotection by
 1496 quercetin: counteracting oxidative stress and more, *Oxidative medicine and cellular longevity*
 1497 2016 (2016).
 1498 [142] R.A. Gismondi, R. Bedirian, C.R. Pozzobon, M.C. Ladeira, W. Oigman, M.F. Neves, Renin-
 1499 angiotensin system blockade associated with statin improves endothelial function in diabetics,
 1500 *Arquivos Brasileiros de Cardiologia* 105 (2015) 597-605.
 1501 [143] N.L. Dal  , M.C. Sosa-Sequera, A. Usubillaga, On the anticonvulsant activity of kaurenic
 1502 acid, *Investigacion Clinica* 48(3) (2007) 349-358.
 1503 [144] J.E. Okokon, P.A. Nwafor, Antiulcer and anticonvulsant activity of *Croton zambesicus*,
 1504 *Pakistan Journal of Pharmaceutical Sciences* 22(4) (2009).
 1505 [145] R. Zadali, M. Baghery, M. Abbasi, N. Yavari, M. Miran, S.N. Ebrahimi, Anticonvulsant activity
 1506 of Iranian medicinal plants and molecular docking studies of isolated phytochemicals, *South*
 1507 *African Journal of Botany* 149 (2022) 646-657.
 1508 [146] J. Folbergrov  , Anticonvulsant action of both NMDA and non-NMDA receptor antagonists
 1509 against seizures induced by homocysteine in immature rats, *Experimental neurology* 145(2)
 1510 (1997) 442-450.
 1511 [147] T. Honor  , J. Lauridsen, P. Krogsgaard-Larsen, The binding of [3H] AMPA, a structural
 1512 analogue of glutamic acid, to rat brain membranes, *Journal of neurochemistry* 38(1) (1982) 173-
 1513 178.
 1514 [148] F. Perez-Vizcaino, J. Duarte, Flavonols and cardiovascular disease, *Molecular aspects of*
 1515 *medicine* 31(6) (2010) 478-494.
 1516 [149] F. Perez-Vizcaino, J. Duarte, R. Jimenez, C. Santos-Buelga, A. Osuna, Antihypertensive
 1517 effects of the flavonoid quercetin, *Pharmacological Reports* 61(1) (2009) 67-75.
 1518 [150] P. Prahalathan, S. Kumar, B. Raja, Effect of morin, a flavonoid against DOCA-salt
 1519 hypertensive rats: a dose dependent study, *Asian Pacific Journal of Tropical Biomedicine* 2(6)
 1520 (2012) 443-448.
 1521 [151] M.R. Santos, F.V. Moreira, B.P. Fraga, D.P.d. Souza, L.R. Bonjardim, L.J. Quintans-Junior,
 1522 Cardiovascular effects of monoterpenes: a review, *Revista Brasileira de Farmacognosia* 21
 1523 (2011) 764-771.
 1524 [152] Y. Hamada, H. Fujii, M. Fukagawa, Role of oxidative stress in diabetic bone disorder, *Bone*
 1525 45 (2009) S35-S38.

1526 [153] H. Ahmadvand, G. Shahsavari, F. Abdolapour, S. Bagheri, The inhibitory effects of Walnut
1527 (*Juglans regia* L.) husk hydroalcoholic extract on LDL oxidation in vitro, *Journal of Jahrom*
1528 *University of Medical Sciences* 9(3) (2011) 1-7.

1529 [154] J. Nakazawa, K. Isshiki, T. Sugimoto, S.I. ARAKI, S. Kume, Y. Yokomaku, M. CHIN-
1530 KANASAKI, M. Sakaguchi, D. Koya, M. Haneda, Renoprotective effects of asialoerythropoietin in
1531 diabetic mice against ischaemia-reperfusion-induced acute kidney injury, *Nephrology* 15(1)
1532 (2010) 93-101.

1533 [155] H. Erdogan, E. Fadillioglu, M. Yagmurca, M. Uçar, M.K. Irmak, Protein oxidation and lipid
1534 peroxidation after renal ischemia-reperfusion injury: protective effects of erdosteine and N-
1535 acetylcysteine, *Urological research* 34 (2006) 41-46.

1536 [156] M.A. Takhtfooladi, A. Asghari, F. Mokhtari, Effect of *Otostegia persica* extract on
1537 ischemia/reperfusion induced renal damage in diabetic rats. A biochemical study, *Acta chirurgica*
1538 *brasileira* 31 (2016) 417-421.

1539 [157] A. Capasso, S. Piacente, C. Pizza, L. Sorrentino, Flavonoids reduce morphine withdrawal
1540 in-vitro, *Journal of pharmacy and pharmacology* 50(5) (1998) 561-564.

1541 [158] W. Lutz, B. Meinrad, S. Andreas, Hepatotoxicity and mechanism of action of haloalkanes:
1542 carbon tetrachloride as a toxicological model, *Critical reviews in toxicology* 33(2) (2003) 105-136.

1543 [159] H. Sadeghi, M.R. Nikbakht, Ghaitasi, Izadpanah., S. Sabzali, Hepatoprotective effect of
1544 *Cichorium intybus* on CCl₄-induced liver damage in rats, *Afr J Biochem Res* 2(6) (2008) 141-144.

1545 [160] S. Sheweita, M. Abd El-Gabar, M. Bastawy, Carbon tetrachloride changes the activity of
1546 cytochrome P450 system in the liver of male rats: role of antioxidants, *Toxicology* 169(2) (2001)
1547 83-92.

1548 [161] K.S. Priya, A. Gnanamani, N. Radhakrishnan, M. Babu, Healing potential of *Datura alba* on
1549 burn wounds in albino rats, *Journal of ethnopharmacology* 83(3) (2002) 193-199.

1550 [162] F. Imperato, Sulphate esters of hydroxycinnamic acid—sugar derivatives from *Adiantum*
1551 *capillus-veneris*, *Phytochemistry* 21(11) (1982) 2717-2718.

1552 [163] M. Alilou, S. Marzocco, D. Hofer, S.F. Rapa, R. Asadpour, S. Schwaiger, J. Troppmair, H.
1553 Stuppner, Labdane-Type Diterpenes from the Aerial Parts of *Rydingia persica*: Their Absolute
1554 Configurations and Protective Effects on LPS-Induced Inflammation in Keratinocytes, *Journal of*
1555 *Natural Products* 83(8) (2020) 2456-2468.

1556 [164] G.C.-F. Chan, W.K. Chan, D.M.-Y. Sze, The effects of β -glucan on human immune and
1557 cancer cells, *Journal of hematology & oncology* 2(1) (2009) 1-11.

1558 [165] R. González, I. Ballester, R. López-Posadas, M. Suárez, A. Zarzuelo, O. Martínez-Augustin,
1559 F.S.D. Medina, Effects of flavonoids and other polyphenols on inflammation, *Critical reviews in*
1560 *food science and nutrition* 51(4) (2011) 331-362.

1561 [166] P. Rathee, H. Chaudhary, S. Rathee, D. Rathee, V. Kumar, K. Kohli, Mechanism of action
1562 of flavonoids as anti-inflammatory agents: a review, *Inflammation & Allergy-Drug Targets*
1563 (Formerly *Current Drug Targets-Inflammation & Allergy*)(Discontinued) 8(3) (2009) 229-235.

1564 [167] M. Hämäläinen, R. Nieminen, P. Vuorela, M. Heinonen, E. Moilanen, Anti-inflammatory
1565 effects of flavonoids: genistein, kaempferol, quercetin, and daidzein inhibit STAT-1 and NF- κ B
1566 activations, whereas flavone, isorhamnetin, naringenin, and pelargonidin inhibit only NF- κ B
1567 activation along with their inhibitory effect on iNOS expression and NO production in activated
1568 macrophages, *Mediators of inflammation* 2007 (2007).

1569 [168] M. Funakoshi-Tago, K. Nakamura, K. Tago, T. Mashino, T. Kasahara, Anti-inflammatory
1570 activity of structurally related flavonoids, Apigenin, Luteolin and Fisetin, *International*
1571 *immunopharmacology* 11(9) (2011) 1150-1159.

1572 [169] J.-H. Lee, H.Y. Zhou, S.Y. Cho, Y.S. Kim, Y.S. Lee, C.S. Jeong, Anti-inflammatory
1573 mechanisms of apigenin: inhibition of cyclooxygenase-2 expression, adhesion of monocytes to
1574 human umbilical vein endothelial cells, and expression of cellular adhesion molecules, *Archives*
1575 *of pharmacal research* 30 (2007) 1318-1327.

1576 [170] S. Chirumbolo, Anti-inflammatory action of isorhamnetin, *Inflammation* 37(4) (2014) 1200-
1577 1201.

1578 [171] Y. Arimura, T. Yano, M. Hirano, Y. Sakamoto, N. Egashira, R. Oishi, Mitochondrial
1579 superoxide production contributes to vancomycin-induced renal tubular cell apoptosis, *Free*
1580 *Radical Biology and Medicine* 52(9) (2012) 1865-1873.

1581 [172] I. Celik, M. Cihangiroglu, N. Ilhan, N. Akpolat, H.H. Akbulut, Protective effects of different
1582 antioxidants and amrinone on vancomycin-induced nephrotoxicity, *Basic & clinical pharmacology*
1583 *& toxicology* 97(5) (2005) 325-332.

1584 [173] F. Öktem, M.K. Arslan, F. Ozguner, Ö. Candir, H.R. Yilmaz, M. Ciris, E. Uz, In vivo
1585 evidences suggesting the role of oxidative stress in pathogenesis of vancomycin-induced
1586 nephrotoxicity: protection by erdosteine, *Toxicology* 215(3) (2005) 227-233.

1587 [174] E. Mazzone, D. Britti, A. De Sarro, A.P. Caputi, S. Cuzzocrea, Effect of N-acetylcysteine on
1588 gentamicin-mediated nephropathy in rats, *European journal of pharmacology* 424(1) (2001) 75-
1589 83.

1590 [175] F. Sharififar, N. Yasa, A. Shafiei, Antioxidant activity of *Otostegia persica* (Labiatae) and its
1591 constituents, (2003).

1592 [176] I.F. Cheng, K. Breen, On the ability of four flavonoids, baicilin, luteolin, naringenin, and
1593 quercetin, to suppress the Fenton reaction of the iron-ATP complex, *Biometals* 13(1) (2000) 77-
1594 83.

1595 [177] C.V. de Whalley, S.M. Rankin, J.R.S. Hoult, W. Jessup, D.S. Leake, Flavonoids inhibit the
1596 oxidative modification of low density lipoproteins by macrophages, *Biochemical pharmacology*
1597 39(11) (1990) 1743-1750.

1598 [178] T.-W. Wu, L.-H. Zeng, J. Wu, K.-P. Fung, Morin: a wood pigment that protects three types
1599 of human cells in the cardiovascular system against oxyradical damage, *Biochemical*
1600 *pharmacology* 47(6) (1994) 1099-1103.

1601 [179] Z. Yu, W.P. Fong, C.H. Cheng, The dual actions of morin (3, 5, 7, 2', 4' -
1602 pentahydroxyflavone) as a hypouricemic agent: uricosuric effect and xanthine oxidase inhibitory
1603 activity, *Journal of Pharmacology and Experimental Therapeutics* 316(1) (2006) 169-175.

1604 [180] M.J. Laughton, P.J. Evans, M.A. Moroney, J.R.S. Hoult, B. Halliwell, Inhibition of mammalian
1605 5-lipoxygenase and cyclo-oxygenase by flavonoids and phenolic dietary additives: relationship to
1606 antioxidant activity and to iron ion-reducing ability, *Biochemical pharmacology* 42(9) (1991) 1673-
1607 1681.

1608

1609