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RHOIFOLIN: A REVIEW OF SOURCES AND BIOLOGICAL ACTIVITIES

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ABSTRACT: Flavonoids are common plant constituents used extensively in phytomedicine to treat a wide range of diseases. Many pharmacological pieces of evidence suggest that flavonoids may play an important role in the decreased risk of chronic diseases associated with a diet rich in plant-derived foods. Therefore, this article focuses on the chemistry, distribution and pharmacological properties of rhoifolin as one of the common and important flavonoids in the plant kingdom. This flavonoid has also been found in several dietary sources such as bitter orange, bergamot, grapefruit, lemon, lupinus, lablab beans, tomatoes, artichoke, bananas, and grapes. Preclinical studies have shown that rhoifolin possesses a variety of significant biological activities including antioxidant, anti-inflammatory, antimicrobial, hepatoprotective and anticancer effects. The literature search was conducted using electronic databases (*e.g.*, Medline, Pubmed, Academic Journals and Springer Link), general web searches were also undertaken using Google applying some related search, journals and scientific theses. The bibliographies of papers relating to the review subject were also searched for further relevant references.

INTRODUCTION: Medicinal plants are well-known biosynthetic laboratories of bioactive substances, thus they can magically provide us with the key to our awful health problems in life. Flavonoids constitute a large group of plant secondary metabolites that enjoy a widespread accumulation throughout the plant kingdom and are commonly found in fruits, vegetables and certain beverages [1]. Chemically, flavonoids are polyphenolic molecules characterized by a diphenylpropane structure (C6-C3-C6) and are found in plants both in a free form and as glycosides.

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During the last decade, flavonoids attracted extensive phytochemical attention and considerable biological interest due to their wide range of pharmacological activities and potentially beneficial effects on human health. They have been reported to have antiviral, anti-allergic, antiplatelet, anti-inflammatory, anti-tumor and antioxidant activities. Recent studies also support a protective effect of flavonoids consumption in cardiovascular diseases and cancer [2].

Apigenin is one of the most common flavonoids present in edible plants and in those used in traditional medicine to treat a wide variety of pathologies. This flavone and its glycosides are widely distributed in the plant kingdom; they are found in many plant families, e.g. Apiaceae, Asteraceae, Fabaceae, Lamiaceae, Malvaceae and Rutaceae [3]. To date, a huge number of apigenin glycosides have been isolated and identified. Many of them were reported to be effective in the pathogenesis of the majority of diseases [4]. Rhoifolin or rhoifoloside is a well-known tri-substituted flavone belongs to the apigenin family. This molecule was obtained for the first time from the fresh leaves of *Rhus succedanea* in 1952 [5]. Several studies have shown that this flavone possesses a variety of pharmacological activities. Accordingly, this work highlights the distribution, chemical, physical, chromatographic and spectral properties as well as the biological effects of rhoifolin.

Chemical, Physical, Chromatographic and Spectral Properties: Chemically, rhoifolin is apigenin 7-*O*-*β*-neohesperidose **Fig. 1** with the chemical formula $C_{27}H_{30}O_{14}$ and the molecular weight 578.53 (exact mass: 578.1636) [3]. It is usually isolated as a yellow amorphous powder or yellow needles (melting at 245-253 °C) after crystallization from methanol or 50% methanol [6, 8]. Rhoifolin is soluble in methanol, hot ethanol and water (water solubility is 2.55 g/L), sparingly soluble in ethyl acetate and cold ethanol and insoluble in *n*-hexane and chloroform [9]. It shows brown or dark purple fluorescence under UV light (254 nm) that turns to yellow upon exposure to ammonia vapors or spraying with 5% aluminum chloride reagent, in addition to yellowish brown color after spraying with 10% sulphuric acid reagent [8]. Different solvent systems can be used for TLC analysis or separation of rhoifolin on silica gel e.g. ethyl acetate-methanol (8:1) [R_f 0.25], ethyl acetate-methanol (8:2) [R_f 0.625], chloroform-methanol (8:2) [R_f 0.36] butanol-acetic acid-water (4:1:1) [R_f 0.53] [6, 9]. $[\alpha]_D^{29}$ −110.0° (*c*, 0.21 in methanol) [6] and in another source −160.0° (methanol) [10].

The IR spectrum of rhoifolin shows bands [ν_{max} (KBr)] at 3388 (OH), 1657 (*α, β*-unsaturated CO), 1605, 1497 and 1488 (aromatic C=C), 1249, 1178 and 1074 (glycosidic C–O) cm^{-1} [7]. UV spectral analysis of rhoifolin shows absorption bands at λ_{max} (log ε) (MeOH): 266 (4.20), 336 (4.30) nm; (NaOMe): 267 (4.20), 387 (4.40) nm; (NaOAc): 257 (4.20), 266 (4.20), 391 (4.40) nm; (NaOAc + H_3BO_3): 268 (4.20), 340 (4.30) nm; ($AlCl_3$): 275 (4.20), 299 (4.10), 350 (4.20), 385 (4.20) nm; ($AlCl_3$ + HCl): 276 (4.20), 298 (4.10), 342 (4.20), 382 (4.10) nm. [7] Its positive HR-ESI-MS shows a pseudomolecular ion peak $[M+H]^+$ at *m/z* 579 [8, 11], whereas $[M-H]^+$ at *m/z* 577 appears in the negative HR-ESI-MS spectrum [12]. ^{1}H-NMR spectrum of rhoifolin in DMSO-d_6 shows the following signals (ppm): 7.91 (2H, d, *J*=8.8 Hz, H-2`,6`), 6.92 (2H, d, *J*= 8.8 Hz, H-3`,5`), 6.84 (1H, d, *J*= 2.0 Hz, H-8), 6.80 (1H, s, H-3), 6.33 (1H, d, *J*= 2.0 Hz , H-6), 5.08 (1H, singlet-like, H-1```), 5.20 (1H, d, *J*= 7.3 Hz, H-1``), 1.16 (3H, d, *J*= 6.3Hz, CH_3-6```). The ^{13}C-NMR spectrum in DMSO-d_6 (ppm): 182.1 (C-4), 164.4 (C-2), 162.6 (C-7), 161.7 (C-4`), 161.1 (C-5), 157.1 (C-9), 128.7 (C-2`,6`), 120.9 (C-1`), 116.2 (C-3`,5`), 105.5 (C-10), 103.2 (C-3), 99.4 (C-6), 94.6 (C-8), sugar moiety: 100.5 (C-1``), 98.2 (C-1```), 77.6 (C-2``), 77.4 (C-3``), 76.8 (C-5``), 72.3 (C-4```), 71.0 (C-2```), 70.8 (C-3```), 71.1 (C-4``), 68.8 (C-5```), 60.9 (C-6``), 18.5 (CH_3-6```) [7]. The HMBC spectrum shows significant correlations between (H-3 and C-2, C-4, C-1`), (H-8 and C-6, C-7, C-9, C-10), (H-1`` and C-7), (H-2`` and C-3``), (H-3`` and C-4``), (H-1``` and C-2``, C-2```, C-5```), (H-4``` and C-5```) and (H-5``` and C-6```) [7].

In another work, small differences ranging from ~ 0.2-0.8 ppm were observed for some carbon signals of the sugar moiety in the same solvent [8]. NMR data of rhoifolin were also recorded in CD_3OD by Yadav *et al.* [11]

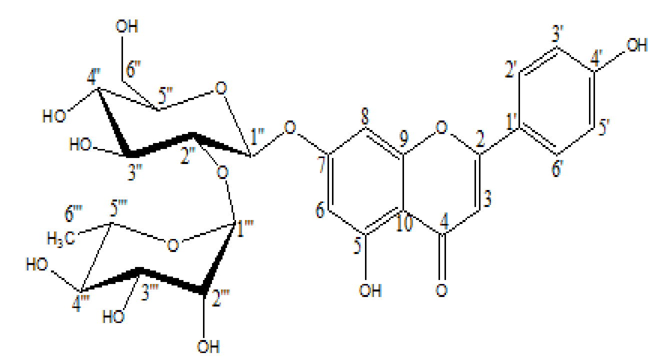

FIG. 1: CHEMICAL STRUCTURE OF RHOIFOLIN

Plant Sources of Rhoifolin: After its first isolation from *Rhus* plants (Anacardiaceae) [5], rhoifolin was isolated from other plant sources belonging to different botanical families. Some edible plants were also found to be rich in this flavone, e.g. bitter orange, bergamot, grapefruit, lemon, lupinus, lablab beans, tomatoes, artichoke, bananas, and grapes. Also, different parts and juices from various *Citrus* spp. are reported to contain rhoifolin in high concentrations [13].

Considerable amounts (up to g/kg) of rhoifolin are also available in different organs of *Chorisia* spp. [6].

Table 1 compiles plant species that contain rhoifolin in alphabetical order.

TABLE 1: A LIST OF PLANT SPECIES CONTAINING RHOIFOLIN

Plant Species	Family	Part (yield)	References
Adinandra nitida Merrill.	Theaceae	Leaf	14, 15
Boehmeria nivea L.	Urticaceae	Leaf	16
Buddleja albiflora Hemsl.	Scrophulariaceae		17
Carduus nutans L.	Asteraceae		18
Chorisia crispiflora H.B.K.	Bombacaceae	Leaf (0.15%), Flower	6, 19
Chorisia insignis H.B.K.	Bombacaceae	Leaf (0.5%)	6
Chorisia pubiflora St.-Hill. Dawson	Bombacaceae	Leaf (0.24%)	6
Chorisia speciosa A. St.-Hill.	Bombacaceae	Leaf (0.27%), Flower	6, 20
Cirsium arvense	Asteraceae		18
Cirsium bitchuense	Asteraceae		18
Cirsium canescense	Asteraceae		18
Cirsium undulatum	Asteraceae		18
Citrus aurantium L (Bigarade or bitter orange)	Rutaceae	Whole plant	3
Citrus bergamia Risso. (Bergamot)	Rutaceae	Whole plant	21
Citrus campestris	Rutaceae	Shoot	22
Citrus grandis L. (*C. maxima* Merr.)	Rutaceae	Leaf (1.1%),	8
		Exocarp of almost ripe fruit (0.090%)	3
Citrus grandis var. *tomentosa*	Rutaceae	Exocarp of ripe fruit (0.655%)	3
Citrus limon (Canton lemon)	Rutaceae	Leaf (9%)	23
Citrus myrtifolia	Rutaceae	Fruit	12
Citrus paradisi Macfad (Grapefruit)	Rutaceae	Leaf	24
Citrus sinensis (Sweet orange)	Rutaceae		21
Cynara scolymus L. (artichoke)	Asteraceae	Flower head	25
Cynodon dactylon	Poaceae		26
Cyperus alopecuroides Rottb.	Cyperaceae	Inflorescence	27
Discocleidion rufescens Franch.	Euphorbiaceae		28
Dolichos lablab L.	Fabaceae	Flower	29
Exochorda racemosa	Rosaceae		30
Festuca argentina Speg.	Poaceae		31
Glechoma hederacea L. (Ground Ivy)	Lamiaceae	Whole plant	32
Gonocaryum calleryanum Baill.	Icacinaceae	Leaf	33
Ilex centrochinensis S.Y.Hu	Aquifoliaceae	Leaf	34
Jatropha curcas Linn.	Euphorbiaceae	Leaf	35
Justicia gangetica L. (*Asystasia gangetica* L.)	Acanthaceae	Leaf	36
Lamiophlomis rotata Benth. (*Phlomis rotata*)	Lamiaceae		3
Ligustrum robustum Roxb.	Oleaceae	Leaf (0.0022%)	37
Lonicera gracilipes var. *glandulosa* Maxim.	Caprifoliaceae		38
Lonicera japonica Thunb.	Caprifoliaceae	Aerial part, flower buds	39, 40
Lupinus spp.	Fabaceae		30
Lupinus luteus (Yellow lupin)	Fabaceae	Seedlings	41
Mallotus nanus Airy Shaw.	Euphorbiaceae	Leaf	42
Musa acuminate (Banana)	Musaceae		43
Marrubium deserti De Noè	Lamiaceae		44
Ononis campestris (Cammock)	Fabaceae	Shoot	16
Ononis spinosa	Fabaceae		45
Oxytropis varians	Fabaceae		46
Paeonia suffruticosa Andrews.	Paeoniaceae	Flower	47
Poncirus trifoliata L.	Rutaceae		48
Prosthechea michuacana W.E. Higgins	Orchidaceae	Bulbs	49
Rhus succedanea L. (*Toxicodendron succedaneum* L.)	Anacardiaceae	Leaf	5
Rhus sylvestris Siebold. & Zucc	Anacardiaceae		3
Sabal serratula (Serenoa or Sabal fruit)	Arecaceae	Whole plant	45
Santalum insulare	Santalaceae	Leaf	50
Saussurea gossypiphora D. Don.	Asteraceae		51

Saussurea medusa Maxim.	Asteraceae		3
Scabiosa comosa Fisch.	Dipsacaceae		52
Scutellaria barbata Don.	Lamiaceae		53
Scutellaria polyodon	Lamiaceae		10
Serenoa repens W. Bartram (Small saw palmetto)	Arecaceae	Fruit	45
Solanum lycopersicum (Tomatoes)	Solanaceae		54
Terminalia arjuna	Combretaceae	Leaf	55
Tilia mongolica Maxim.	Tiliaceae		56
Trachelospermum difforme	Apocynaceae		57
Trachelospermum jasminoides (Lindl.) Lem.	Apocynaceae		57
Uraria picta	Fabaceae	Aerial parts	11
Veronica francispetae M. A. Fischer	Plantaginaceae		58
Veronica persica Poir.	Plantaginaceae		58
Veronica polita Fries	Plantaginaceae		58
Veronica siaretensis Lehmann	Plantaginaceae		58
Vitis vinifera	Vitaceae		59

Isolation of Rhoifolin from *Chorisia* spp.: Different organs of *Chorisia* spp. (Bombacaceae) are a well-known and rich source of rhoifolin. Substantial amounts of this glycoside can be directly obtained from the total alcoholic and aqueous extracts of these plants. Four *Chorisia* spp. growing in Argentina provided rhoifolin in different yields including *C. insignis* (0.5%), *C. speciosa* (0.27%), *C. pubiflora* (0.24%) and *C. crispiflora* (0.15%) [6]. According to the method described by Coussio, [6] 1 kg of fresh leaves of *C. insignis* was boiled for 15 min with 2.6 l of water, and the extract was filtered on hot. Rhoifolin was then crystallized on cooling the filtrate. Further purification was achieved by several recrystallization steps from 50% methanol to provide yellow needles sintering at 202-205 °C and melting at 245 °C [6].

In another work by Eldahshan, the air-dried powdered leaves of *C. crispiflora* (1kg) was extracted with 70% ethanol. The extract was then entirely dried and dissolved in a small amount of distilled water and partitioned with *n*-hexane, ethyl acetate, and butanol, successively. The aqueous residue was dried and extracted with methanol at 40 ºC. The methanol extract upon concentration yielded yellow crystals of rhoifolin (8.3 g) that was purified by further crystallization [7].

HPLC Analysis and Quantification of Rhoifolin: In a study by Scordino *et al.* to investigate the identity and relative distribution of flavonoids and furocoumarins in pulp and peel tissues of the unripe *Citrus myrtifolia* by HPLC/PDA/ESI/MS-MS, rhoifolin was identified and quantified as 0.4% in the pulp and 1.6% in the peel. It also showed retention time of 40.0 min in HPLC analysis using a binary gradient of 0.3% formic acid in water and 0.3% formic acid in acetonitrile on an analytical column (Luna C18 250 × 4.6 mm, 5 μm i.d. (Phenomenex)) and photodiode-array detector [12].

On the other hand, a method for determining flavonoids in human plasma was presented for application to pharmacokinetic studies of rhoifolin. Isocratic reversed-phase HPLC was used with genistin as an internal standard and solid-phase extraction using a Sep-Pak C18 cartridge. A mobile phase of acetonitrile-0.1M ammonium acetate solution (20:80 v/v) was used [59].

In another work, an LC method was developed for quantitation of rhoifolin in *Uraria picta*. Rhoifolin showed a retention time of 14.74 min in the isocratic RP-LC method using a C18 column and a mobile phase of acetonitrile-water containing 1.0% trifluoroacetic acid (TFA) (20:80 v/v). A flow rate of 1.0 ml min^{-1} and column temperature at 30 °C were maintained throughout the run. The quantitation was performed at 265 nm [11].

Biological Activities:

Anti-inflammatory Activity: In a study by Eldahshan and Azab, rhoifolin was shown to possess potent anti-inflammatory activity at low doses. It caused a time- and reverse the dose-dependent reduction of carrageenan-induced rat paw edema. Following 4 hr of treatment, rhoifolin at doses of 2.5, 25 and 250 mg/kg caused a significant inhibition of rat paw edema volume by 14, 25 and 45%, respectively in comparison to the control group (74%). In addition to significantly abrogating prostaglandin E2 level, increasing doses of rhoifolin significantly diminished the TNF-α release in the inflammatory exudates. In the same animal model, rhoifolin increased the total antioxidant capacity in a reverse dose order, with the highest capacity obtained with the lowest dose tested [61].

Anticancer Activity: Rhoifolin exhibited potent *in-vitro* cytotoxicity with great selectivity against human epidermoid larynx (Hep 2) (IC_{50} = 5.9 μg/ml) and human cervical (HeLa) carcinoma cell lines (IC_{50} = 6.2 μg/ml). Promising activities were also obtained against hepatocellular (Hep G2) (IC_{50} 22.6 μg/ml), colon (HCT-116) (IC_{50} 34.8 μg/ml) and fetal human lung fibroblast (MRC-5) (IC_{50} = 44.6 μg/mL) carcinoma cell lines. The effects were nearly similar to those of vinblastine. Results also showed no cytotoxic activity against healthy normal mammalian cells (Vero cells) indicating a high degree of selectivity [7].

Anti-diabetic Activity: In differentiated 3T3-L1 adipocytes, rhoifolin showed a dose-dependent insulin-mimetic effect within the concentration range 0.001-5 μM. At 0.5 μM, rhoifolin showed a nearly similar response to that of 10 nM of insulin on adiponectin secretion level. Furthermore, 5 μM of rhoifolin showed equal potential with 10nM of insulin to increase the phosphorylation of insulin receptor-β, in addition to its positive effect on GLUT4 translocation. These findings indicated that rhoifolin might be beneficial for diabetic complications through enhanced adiponectin secretion, tyrosine phosphorylation of insulin receptor-β and GLUT4 translocation [8].

Hepatoprotective Activity: Rhoifolin isolated from *Chorisia crispiflora* H.B.K. leaves showed 80.3% protection against CCl_4-induced hepatotoxicity in mice at 20 mg/Kg. The liver showed its normal architecture and the serum levels of ALT and AST were kept close to normal [62]. In another study, pretreatment of CCl_4-treated rats with rhoifolin reduced the enhanced serum levels of hepatic enzymes. AST, ALT, TB, ALP and total serum protein were reduced by 60%, 59%, 51%, 39%, and 43%, respectively, indicating good anti-hepatotoxic activity. Also, the elevated level of lipid peroxidation products (TBARS), an indicator of oxidative stress in CCl_4-intoxicated mice, was depressed by oral administration of rhoifolin at 20 mg/kg. The effect was comparable to that of silymarin [49].

Antihypertensive and Hemodynamic Effects: It was reported that rhoifolin exhibited important antihypertensive effects in conscious spontaneously hypertensive rats [3]. In another study, the *in-vitro* ACE inhibitory activity of 17 flavonoids belonging to five structural subtypes were evaluated at two concentrations (500 and 100 μM) by a fluorimetric method. Among them, rhoifolin exhibited IC_{50} value of 183 μM. The catechol group of ring B, the double bond between C-2 and C-3 of ring C and the ketone group at C-4 of ring C were found to be important structural requirements for such activity [63].

On the other hand, the acute effects of luteolin, apiin and rhoifolin on the pulmonary vascular circuit in two experimental models of pulmonary hypertension, produced by hypoxia and by prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) in anesthetized dogs, were studied in comparison with nifedipine. Rhoifolin at 5 mM/kg/i.v. produced no change in hypoxic pulmonary vasoconstriction but decreased cardiac output and aortic pressure. The response of pulmonary hypertension induced by $PGF_{2\alpha}$ to flavonoids and nifedipine was nearly identical to that of hypoxia-induced pulmonary hypertension [64]. In another comparative study of the hemodynamic effects of rhoifolin and vitexin in anesthetized dogs, rhoifolin caused a decrease of mean aortic pressure, of the arterial and pulmonary capillary pressure and heart rate [65].

Antimicrobial Activity: Rhoifolin exhibited certain inhibitory activity against *Escherichia coli* [28]. This flavone was also found to cause 13% inhibition of coxsackievirus B3 infection with IC_{50} of 569.05 μM, whereas it reduced the viability of untreated cell cultures by 50% at >1000 μM in MTT assay with a calculated selective index of 1.8. Its antiviral mechanism may be due to the prevention of virus adsorption onto the cell surface, inhibition of protein kinase, viral DNA synthesis or virus-associated reverse transcriptase [66].

A composition comprising ligustroflavone, rhoifolin, and hyper in was found to potentially inhibit the influenza virus neuraminidase from hydrolyzing the sialic acid on the cell surface, prevent the virus from combining with the cell surface receptors and entering into the cells and reduce the generation of the virus within the cells, thus effectively and specifically inhibiting influenza virus replication. Besides, this composition overcomes the side reactions of the existing drugs [67].

Other Activities: In work to evaluate the inhibition of quinine 3-hydroxylation (CYP3A4 activity) in two human liver microsomes (HL1 and HL2) by grapefruit flavonoids, furanocoumarins and coumarins; rhoifolin did not inhibit the metabolism of quinine at 10 and 100 μM. Only a moderate inhibition (18% for HL1 and 26.1% for HL2) was observed at 200 μM [68]. On the other hand, rhoifolin at 100 μmol/l inhibited CCl_4- and FeSO4+cysteine-induced lipid peroxidation by 37.9% and 70.1%, respectively, with IC_{50}= 66.1 μmol/l. Additionally, it exhibited inhibitory effects on AAPH-induced hemolysis of RBCs with IC_{50}= 95.9 μmol/l indicating its potential antioxidant properties [3]. It was also reported that rhoifolin possess xanthinoxidase inhibitory effect (12.9%) at 50 μg/ml [3].

CONCLUSION: Due to the growing demand for safe, natural pharmaceuticals to face the everyday challenging diseases and in light of the considerable interest in the chemistry and pharmacological properties of flavonoids, we have undertaken this review to summarize the chemistry, distribution and biological activities of rhoifolin. The available literature data have shown that this flavone enjoys a wide distribution in several plant families and can also be obtained in considerable amounts from some species, *e.g. Citrus* and *Chorisia* spp. Moreover, numerous preclinical studies have shown that rhoifolin possesses a wide range of biological activities and several possible mechanisms of action have been elucidated.

These pharmacological findings strongly recommend that rhoifolin could be developed into widely used remedies especially for its potent anti-inflammatory, hepatoprotective, insulin-mimetic actions and the highly selective cytotoxic effects. Hence, further investigation of the molecular mechanisms of these effects along with detailed clinical studies will be necessary for the future.

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