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Traditional Medicinal Uses, Phytochemicals, and Pharmacological Activities of Genus *Rhamnus*: A review

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Abstract: The genus *Rhamnus* belongs to the Rhamnaceae family, which contains approximately 137 species, traditionally used as folk medicine in East Asia, North and South America, and subtropical regions of Africa. The genus is used traditionally to treat diseases such as cancer, wound, jaundice, hepatitis, gonorrhea, laxative, hypertension, malaria, stomach ache, snake bite and diarrhea. Anthraquinones and flavonoids are the most cited compounds from the genus of which polyphenols were abundant with tremendous antioxidant, wound healing and antiinflammatory activities. Pharmacological activity evaluation of the extracts and isolated compounds revealed anti-inflammatory, antioxidant, antimalarial, antibacterial, anti-mutagenic, anti-genotoxic, hepatoprotective, anticancer, and anti-proliferative activity. The genus afforded drug leads such as 6-methoxysorigenin (**12**) and prinoidin (**23**) with anti-tyrosinase and cytotoxicity, respectively, as well as antioxidant drug leads such as Kaempferol-3-O-β-rhamninoside (**31**) rhamnetin-3-*O*-*β*-isorhamninoside (**37**) and isotorachrysone (**55**). The present review endeavors to provide a comprehensive and up to date compilation of documented traditional medicinal uses, phytochemicals and pharmacological activities of the genus and provided valuable information in support of its uses as an alternative medicine for future healthcare practice.

Keywords: *Rhamnus*, anthraquinones, flavonoids, pharmacological activities.

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INTRODUCTION

Traditional medicine has been in existence even before the advent of modern medicine. It continues to remain as an alternative care available for the majority of the developing countries due to its intrinsic qualities, unique, and holistic approaches as well as its accessibility and affordability (1, 2). The genus *Rhamnus* consists of 137 species (Figure 1) and 19 synonyms (3). The word *Rhamnus* means 'a kind of prickly plant' and 'buckthorn or Christ's thorn' in Greek and Latin languages (4). The genus is distributed in East Asia, North and South America and various parts of subtropical Africa with a wide spectrum of traditional medicinal uses (5-13).

The chemistry of *Rhamanus* species does not exhibit great diversity. The main groups of secondary metabolites reported from the genus are anthrones, anthraquinones, and flavonoids of which polyphenols were abundant with tremendous antioxidant, wound healing, and antiinflammatory activities. The present review endeavors to provide a comprehensive and up-to-date compilation of documented biological activities and phytochemistry of the genus and provided valuable information in support of its uses as an alternative medicine for future healthcare practice.

Figure 1: Some medicinally important species of the genus *Rhamnus* L. (14, 15).

Taxonomy of the genus *Rhamnus*:

Kingdom: *Plantae*, **Order**: *Rosales*, **Family**: *Rhamnaceae*, **Genus**: *Rhamnus*. The names redberry, red berry buckthorn, California redberry, evergreen buckthorn, spiny buckthorn, and holly leaf buckthorn have been used for multiple taxa of *Rhamnus* (16).

Botanical Description and Traditional Uses

The genus *Rhamnus* comprises 137 species of shrubs and small trees in temperate, sub-tropical and tropical countries (17). It is an evergreen or deciduous plant and resistant to frost. The leaves are either alternate or sub-opposite. The hermaphrodite small flowers are weakly scented (18). Botanical description and traditional uses of various *Rhamnus* species is summarized in Table 1 below.

Table 1: Botanical distribution and traditional medicinal uses of the genus *Rhamnus.*

Scientific name	Part	Distribution	Traditional use	Refs
R. alaternus L.	Leaf, Aerial Part,	Algeria	as a digestive, diuretic, laxative, and for the therapeutics of hepatic and dermatological disorders	(19)
	Leaf	Algeria	treatment of gastrointestinal system diseases (hepatitis)	(20)
	Bark	Algeria	Used to treat jaundice	(21)
	Aerial part	Algeria	Hepatic jaundice and chlorosis	(22)
	Root, Aerial Part	Spain, Iberian Peninsula	Used to treat depurative (blood purification)	(23, 24)
	Aerial Part	Spain	therapeutics of hypercholesterolemia	(23)
	Aerial Part	Spain	therapeutics of antihypertensive (lowers blood pressure)	(23)
	Bark, Branch	Italy	to treat hemostatic, wounds, laxative	(25)
	Branch, leaf	Iberian Peninsula	to treat high blood pressure	(24, 26)
	Branch, Leaf	Israel, Algeria	to treat jaundice	(5, 22)
R. alnifolia L'Hér	Root, Bark	USA	to treat gonorrhea and cathartic	(7)
R. alpina L.	Branch	Italy	to treat cardiac disease, wounds	(27)
R. cathartica L.	Bark	Bosnia and Herzegovina, Turkey	treatments of common buckthorn, diarrhea, diuretic	(28, 29)
	Fruit	Southeast Europe	antiseptic for wounds	(30)
	Fruit	Serbia	to treat laxative	(31)
R. fallax L.	Bark	Bosnia and Herzegovina	to treat and manage dermal diseases	(32, 33)
	Bark	Montenegro/ Serbia	to treat constipation	(34)
R. heterophylla Oliver	Root, Leaf	China	to cease bleeding	(11)
R. ilicifolia Kellogg	Root	USA	laxative, diuretic and to treat gonorrhea	(16)
	Whole Part	USA	analgesic or antirheumatic	(35)
R. lycioides L.	Leaves, Shoot	Turkey	to treat pulmonary cancer	(36)
R. nepalensis Wall MA Lawson	Root	India	to treat the treatment of pneumonia	(37)
R. nitudus Davis	Bark	Turkey	Used as emetic	(38)
R. persica Boiss.	Leaf	Iran	to treat allergy and itching in children, wound	(39)
R. prinoides L'Hér	Bark, Fruit, Multiple Part	Kenya	to treat sexually transmitted disease (gonorrhea),	(40)
	Fruit, Stem, Root, and Leaf	Kenya	to treat gonorrhea, prostate, malaria, brucellosis	(41)
	Root	Kenya	to treat muscular skeleton disorder (Arthritis, backaches, rheumatic)	(42)
	Leaf	Ethiopia	to treat Snakebite	(43)
	Roots, Leaf	South Africa	Used for blood purifiers, pneumonia, emetics, purgative, colic,	(44)

			stimulants	
	Branch	South Africa	Herpes, diabetes, HIV related infections	(45)
	Root, Leaf, and Steam	Kenya	to treat ear, nose, and throat (ENT) diseases	(46)
	Leaf	Ethiopia, Uganda	to treat tonsillitis, wound, eczema, skin infection, fever in children, tuberculosis, dandruff, water-borne disease	(47-56)
	Seed	Ethiopia	to treat ringworm	(57)
	Root	Kenya	to treat sexually transmitted infection	(58)
	Root	Kenya	amoebiasis, bacillary dysentery, tonic, pneumonia	(59)
	Root	Ethiopia	to treat hepatic problems	(60)
R. purpureus Edgew.	Bark, Steam, Fruit, Leaf	Himalayas	to treat digestive disorders	(61, 62)
R. purshiana DC.	Bark	Algeria	to treat respiratory tract diseases (pharyngitis)	(20)
	shell	Mexico	to treat skin rash and stomachache	(63)
R. staddo A.Rich	Tree	Kenya	Used for strength/nutrient supplement, sexually transmitted diseases, flu/cold	(64)
	Multiple Part	Kenya	to treat diarrhea	(40)
	Root, Steam,	Kenya	to treat gonorrhea, diabetes, endometritis	(41)
R. triqueter Wall M. A. Lawson	Leaf, Fruit, Branch	Pakistan	to treat hemorrhagic septicemia	(65)
	Bark, Fruit	Himalaya	used for blood purifier, boils, scabies, skin diseases, tonic	(62)
R. virgatus Roxb.	Bark	Himalaya, India	to treat eczema and ringworms	(61, 66)
	Steam, Fruit, Bark	Himalaya	to treat emetic, purgative, eczema, ringworm, affection of spleen	(62)
	Fruit and Bark	Nepal/Iran	to treat diarrhea and dysentry	(67)
	Fruit, Bark	India	to treat emetic, spleen infection, and purgative, curing white dots of eyes	(61, 68)

Phytochemicals

Anthraquinones, flavonoids, naphthalene derivatives, terpenoids, alkaloids, steroids, organic acids are secondary metabolites reported from various *Rhamnus* species of which anthraquinones and flavonoids are the most cited ones (Figures 2-4, Table 2).

Anthraquinones

Several anthraquinones (**1-30**, Table 2) have been isolated from *Rhamnus* species. Of these, compounds, a cytotoxic compound prinoidin (**23**) was reported from the fruits of *R. nepalensis* against KB (human epidermoid carcinoma of the mouth) with IC_{50} value of 0.045 μM, which was four times more potent than the standard doxorubicin having IC_{50} value of 0.2 μM (69). A prominent anti-tyrosinase effect was displayed by 6-methoxysorigenin (**12**) reported from *R. nakaharai* with IC_{50} vaue of 42.2 μM, which was twofold more potent than kojic acid with IC_{50} value of 82.1 μM (70). In a related study, antioxidant alaternin (**10**) was reported from *R. nakaharai* with IC_{50} value of 117.7 μM compared to ascorbic acid (IC_{50} value of 63.7 μM) using DPPH assay method (70).

Flavonoids

Flavonoids, which are important secondary metabolites, are widespread in the plant kingdom, either in a free form or in the form of glycosides with wide spectrum of pharmacological application (71). Various flavonoids (**31–52)** and their derivatives have been reported from the genus *Rhamnus*. Of these, flavonoids **31**, **33**, **36**, **37** and **40** exhibited cytotoxic, antioxidant, anti-hyperlipidemia, anti-proliferative, and anti-genotoxic activity (72-75).

Naphthalene derivatives

To date, 7 naphthalene derivatives (**53**-**59**) have been reported from different parts of *Rhamnus* species such as *R. prinoides*, *R. cathartica*, *R. wightii*, *R. procumbens*, *R. makaharai*, *R. pallasri* and *R. serrutu*. Of these, musizen (**54**) obtained from whole part of *R. wightii* exhibited antibacterial activities against *S. aureus* and *K. pneumonia* using agar disc diffusion assay with MIC value of 9 μg/mL, which was more potent than streptomycin having MIC value of 120 μg/mL (76).

Terpenoids

Up to date, four terpenoids (**60-63**) have been reported from leaves and bark extracts of *R. californica* (77).

Alkaloids

Alkaloids are a large group of naturally occurring compounds with diverse pharmacological activity (78). To date, four alkaloids (**64-67**) have been reported from leaves and bark extracts of *R. californica* (77).

Steroids

Previous studies reported limited number of steriods and steriod glycosides such as β-sitosterol (**68**) from roots of *R. formosana*, root bark and leaves of *R. alaternus* and leaves of *R. serrutu* (79-81) whereas stigmasterol-*β*-D-glycoside (**69**) and β-sitosterol-3-*O*-glycoside (**70**) were reported roots of *R. formosana* (79) and root bark and leaves of *R. alaternus* (80), respectively.

Organic acids

Organic acids are another important component of the genus *Rhamnus*. Previously studied revealed compounds **71-72** and **73**-**75** from leaves of *R. alaternus* (82) and leaves of *R. heterophylla* (83), respectively.

Miscellaneous Compounds

Compounds **76** and **77** were reported from root and bark of *R. serrutu* and *R. davurica*, respectively (81, 84). The later was also reported from heart wood parts of *R. nakaharai* (70).

Table 2: Compounds reported from the genus *Rhamnus.*

Compound	Plant species	Part used	Reference
Anthraquinones			
Chryisophanol (**1**)	*R.formosana* and *R. serrata*	Root	(79, 81)
	R.prinoides	Leaves, Stem	(85)
	R.alaternus	Stem, bark	(86)
	R.frangula	Stem bark and branch	(87)
	R.sphaerosperma	Stem	(88)
	R.alpinus and *R.saxatilis*	Bark	(89-91)
	R.nepalensis	Fruit	(69)
	R.californica	Leaf and bark	(77)
Emodin (**2**)	*R.formosana*and *R. serrata*	Root	(79, 81)
	R.pumila	Stem,bark	(86)
	R.prinoides	Fruit, Leaf	(92, 93)
	R.cathartica, *R.pubescens*, *R. alaternus* and *R.heterophylla*	Leaf	(83, 94-96)
	R.frangula	Stem bark and branch	(87)
	R.sphaerosperma	Stem	(88)
	R.procumbens	Whole part	(97)
	R.alpinus and *R.saxatilis*	Bark	(89, 90)
	R.nakaharai	heartwood	(70)
	R.nepalensis	Fruit	(69)
	R.californica	Leaf and bark	(77)
Physcion (**3**)	*R.formosana*	Root	(79)
	R.fallax	Stem, bark	(86)
	R.intermedia	Stem	(86)
	R.prinoides	Leaf and Stem	(85, 92)
	R.frangula	Stem bark and branch	(87)

	R.serrate, R.alaternus and *R. alaternus*	Root	(81, 98)
	R.sphaerosperma	Stem	(88)
	R.davurica, R.alpinus and *R.saxatilis*	Bark	(84, 89, 91)
	R.procumbens	Whole part	(97)
	R.nepalensis	Fruit	(69)
	R.californica	Leaf and bark	(77)
Emodinanthrone (**4**)	*R.prinoides*	Leaves, Stem	(85, 93)
Emodinbianthrone (**5**)	*R.prinoides*	Fruits	(93)
	R.nepalensis	Fruit	(69)
Chrysophanol-emodinbianthrones (**6**)	*R.nepalensis*	Fruit	(69)
Chrysophanolbianthrone (**7**)	*R.nepalensis*	Fruit	(69)
1,2,6,8-tetrahydroxy-3-methylanthraquinone-8-O-β-glucopyranoside (**8**)	*R.nakaharai*	heartwood	(70)
emodin-8-O-β-glucopyranoside (**9**)	*R.nakaharai*	heartwood	(70)
Alaternin (**10**)	*R.nakaharai*	heartwood	(70)
6-methoxysorigenin-8-O-β-glucopyranoside (**11**)	*R.nakaharai*	heartwood	(70)
6-methoxysorigenin (**12**)	*R.nakaharai*	heartwood	(70)
Aloe-emodin (**13**)	*R.alaternus*	Root	(98)
	R.alpinus and *R.saxatilis*	Bark	(89-91)
Rhein (**14**)	*R.alaternus*	Root	(98)
	R.alpinus and *R.saxatilis*	Bark	(89-91)
Madagascin (**15**)	*R.saxatilis* and *R. alpinus*	Bark	(90)
	R.cathartica and *R. intermedia*	Fruit	(99)
3-geranyloxyemodin (**16**)	*R.saxatilis and R. alpinus*	Bark	(90)
emodin-6-O-arabinopyranoside-3',4'-diacetate (**17**)	*R.alaternus*	Fruit	(100)
emodin-6-O-arabinopyranoside-2',3',4'-triacetate (**18**)	*R.alaternus*	Fruit	(100)
Emodin 6-O-β-L-rhamnose (**19**)	*R.libanoticus*	Bark	(101)
Emodin 8-O-β-D-glucoside (**20**)	*R.libanoticus*	Bark	(101)

Physcion 8-O-β-rutinoside **(21**)	*R.libanoticus*	Bark	(101)
	R.pallasri	Bark	(102)
Emodinanthrone-6-O-rhamnopyranoside-2',3',4'-triacetate (**22**)	*R.prinoides*	Fruit	(93)
Prinoidin (**23**)	*R.prinoides*	Fruit	(85, 93)
Prinoidin-emodinbianthrones (**24**)	*R. nepalensis*	Fruit	(69)
Rhamnepalins (**25**)	*R. nepalensis*	Fruit	(69)
Glucofrangulin (**26**)	*R.prinoides*	Fruit	(103)
	R.cathartica	Leaf	(94)
1,6,8-trihydroxy-3-methylanthraquinone 1 -O-rhamnosyl (1→2) glucoside (**27**)	*R.formosana*	Root	(104)
1,8-dihydroxy-6-methoxy-3- methyl anthraquinones 8-0- rhamnosyl-(1→2)-glucoside (**28**)	*R.formosana*	Root	(79)
1,2,6,8 tetrahydroxy-3 methyl anthraquinone 8-O-ß-D-glucopyranoside (**29**)	*R.alaternus*	Root bark and Leaf	(80)
1,4,6,8 tetrahydroxy-3 methyl anthraquinones 1-O-ß-D-glucopyranosyl-4,6-di-O-α-L-rhamnopyranoside (**30**)	*R.alaternus*	Root bark and Leaf	(80)
Flavonoids			
Kaempferol-3-O-β-rhamninoside (**31**)	*R.petiolaris*	Fruit	(105)
	R. nakaharai	Heartwood	(70)
	R. alaternus	Leaf	(72, 73)
Luteolin (**32**)	*R.alaternus*	Leaf	(82)
	R.davurica	Bark	(84)
Kaempferol (**33**)	*R.alaternus*	Leaf, Fruit	(96, 106)
	R.lycioides	Aerial parts	(107)
	R.davurica	Bark	(84)
	R.saxatilis, R.catharticus and *R.disperma*	Fruit	(106)
	R.californica	Leaf and bark	(77)
	R.pallasii	Bark	(108)

	R.heterophylla	Leaf	(83)
Quercetin (**34**)	*R.lycioides*	Aerial part	(107)
	R.pallasii and *R.davurica*	Bark	(84)
	R.saxatilis, R.catharticus, R.alaternus and *R.disperma*	Fruit	(106)
	R.californica	Leaf and bark	(77)
	R.heterophylla	Leaf	(83)
Rhamnazin-3- isorhamninoside (**35**)	*R.formosana*	Root	(104)
Rhamnocitrin 3-O-β-isorhamninoside (**36**)	*R.formosana*	Root	(104)
	R.nakaharai	heartwood	(70)
	R. alaternus	Leaf	(72, 73)
Rhamnetin 3-O-isorhamninoside (**37**)	*R. alaternus*	Leaf	(72, 73)
Rhamnetin 3-O-(3””-O-β-coumaroyl)-β – rhamninoside (**38**)	*R.petiolaris*	Fruit	(105)
Quercitrin **39**)	*R.petiolaris*	Fruit	(105)
	R.pallnsii	Bark	(108)
Apigenin (**40**)	*R.davurica*	Bark	(84)
Rutin (**41**)	*R.alaternus*	Leaf	(82)
	R.cathartica	Leaf	(94)
Rhamnazin (**42**)	*R.prinoides*	Fruits, Leaf	(93)
	R.lycioides	Arial part	(107)
	R.disperma	Arial part	(109)
	R.heterophylla	Leaf	(83)
Rhamnetin (**43**)	*R.lycioides*	Arial Part	(107)
	R.disperma	Fruit	(70)
Aromadendrin (**44**)	*R.lycioides*	Arial Part	(110)
	R.pallasii	Bark	(108)
Eriodictyol (**45**)	*R.lycioides*	Arial Part	(110)
	R.pallasii	Bark	(108)
Rhamnocitrin (**46**)	*R.prinoides*	Leaf and Stem	(93)
	R.lycioides	Arial Part	(107)
	R.davurica	Bark	(84)
	R.saxatilis	Fruit	(106)

	R.catharticus	Fruit	(106)
	R.alaternus	Fruit	(106)
	R.heterophylla	Leaf	(83)
Taxifolin (**47**)	*R.lycioides*	Arial Part	(107)
	R.pallnsii	Bark	(108)
	R.davurica	Bark	(84)
	R.pallasii	Bark	(108)
3- methoxy flavone (**48**)	*R.lycioides*	Aerial part	(107)
3-O-Methylquercetin (**49**)	*R.prinoides*	Leaf and Stem	(93)
Pallasiin (**50**)	*R.pallasii*	Bark	(108)
Isorhamnetin (**51**)	*R.pallasii*	Bark	(108)
Mearnsetin (**52**)	*R.pallasii*	Bark	(108)
Naphthalene Derivatives			
Geshoidin (P-sorigenin-8-O-β-D-glucoside) (**53**)	*R.prinoides*	Leaf and stem	(85)
	R. cathartica	Leaf	
Musizin (**54**)	*R.prinoides*	Leaf and stem	(85)
	R.wightii and *R. procumbens*	Whole part	(76, 97)
Isotorachrysone (**55**)	*R.nakaharai*	Root bark	(111)
β-sorigenin (**56**)	*R.prinoides*	Leaf and stem	(85)
	R. cathartica	Leaf	(94)
α-sorinin (**57**)	*R.pallasri*	Bark	(102)
Eugenine (**58**)	*R.serrutu*	Root	(81)
3-hydroxyeugenine (**59**)	*R.serrutu*	Root	(81)
Terpenoids			
Umbellulone (**60**)	*R.californica*	Leaf and bark	(77)
1,8-cineole (**61**)	*R.californica*	Leaf and bark	(77)
α-terpineol (**62**)	*R.californica*	Leaf and bark	(77)
Thymol (**63**)	*R.californica*	Leaf and bark	(77)
Alkaloid			
Domesticine (**64**)	*R.californica*	Leaf and bark	(77)
Nordomesticine (**65**)	*R.californica*	Leaf and bark	(77)

Isoboldine (**66**)	*R.californica*	Leaf and bark	(77)
Bufotenine (**67**)	*R.californica*	Leaf and bark	(77)
Steroids			
Stigmasterol-β-D-glycoside (**68**)	*R.formosana*	Root	(79)
β-sitosterol (**69**)	*R.formosana*	Root	(79)
	R.alaternus	Root bark and Leaf	(80)
	R.serrutu	Leaf	(81)
β-sitosterol-3-O-glycoside (**70**)	*R.alaternus*	Root bark and Leaf	(80)
Organic Acid			
P-coumaric acid (**71**)	*R.alaternus*	Leaf	(82)
Ferulic acid (**72**)	*R.alaternus*	Leaf	(82)
Gallic acid (**73**)	*R.alaternus*	Leaf	(82)
	R.heterophylla	Leaf	(83)
Malic acid (**74**)	*R.heterophylla*	Leaf	(83)
Salicylic acid (**75**)	*R.heterophylla*	Leaf	(83)
Miscellaneous Compounds			
5-hydroxy-7-methoxyphtali (**76**)	*R.serrutu*	Root	(81)
	R.davurica	Bark	(84)
p-hydroxybenzaldehyde (**77**)	*R. nakaharai*	Heart wood	(70)

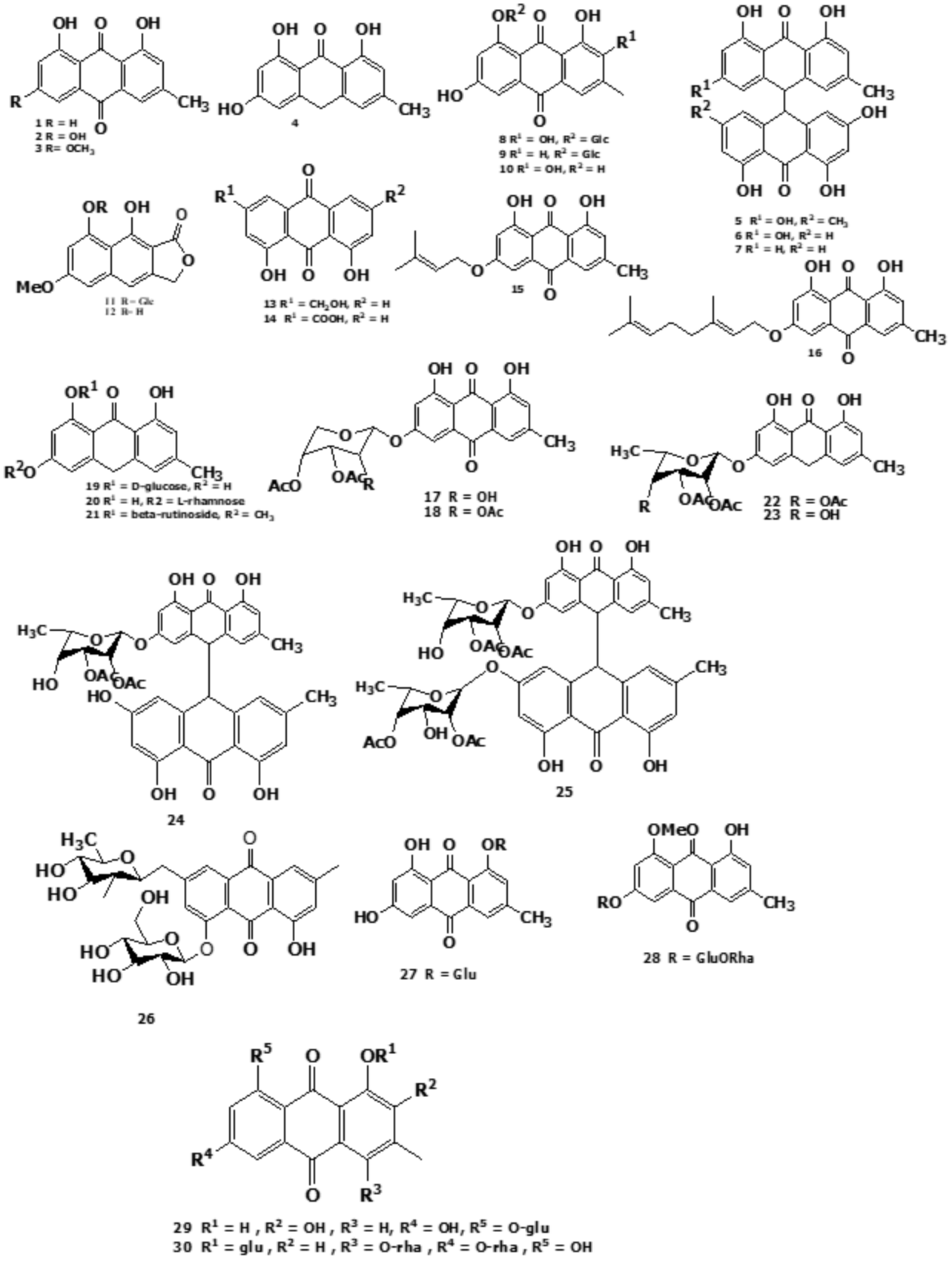

Figure 2: Anthraquinones reported from the genus *Rhamnus.*

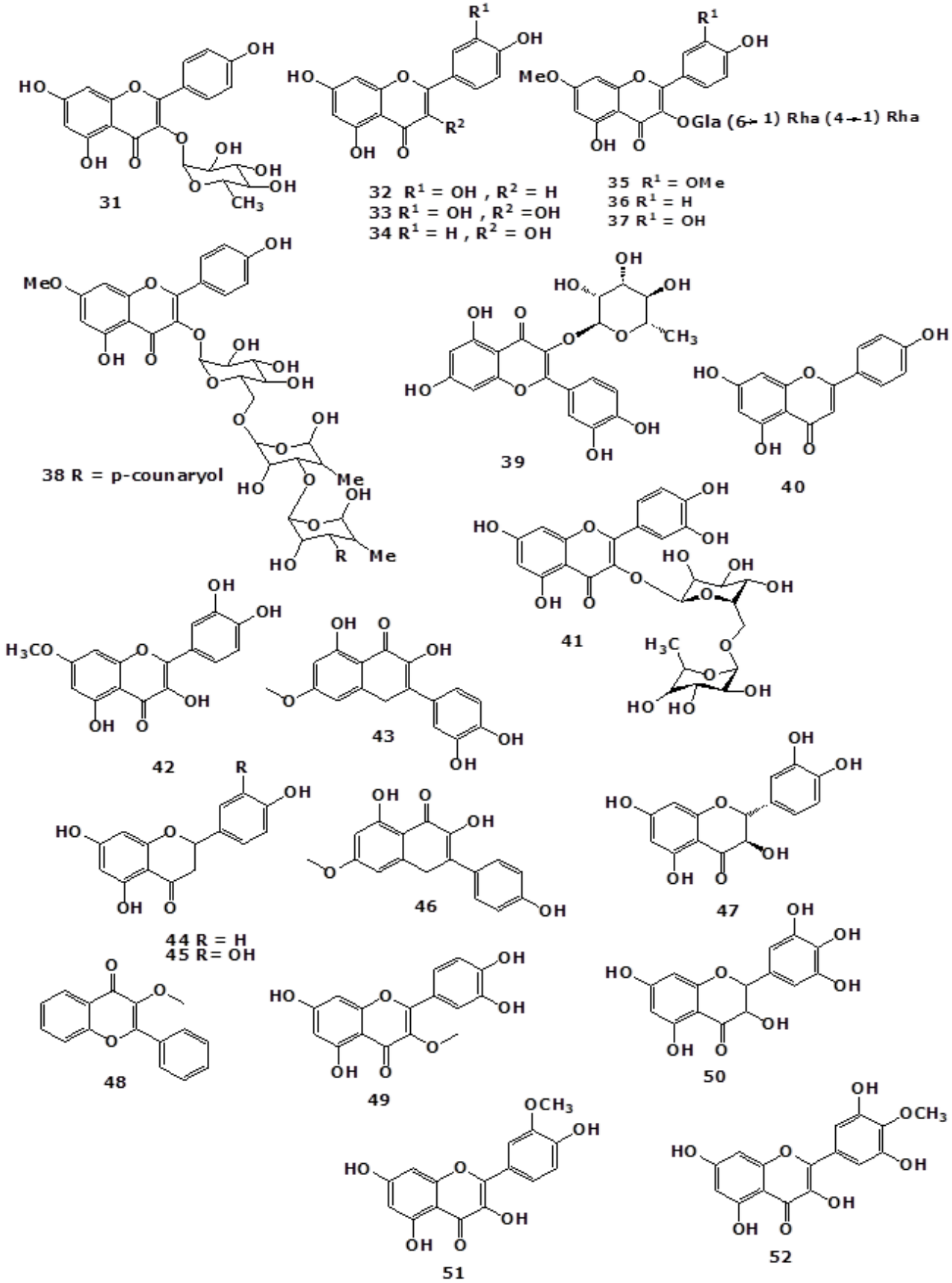

Figure 3: Flavonoids reported from the genus *Rhamnus.*

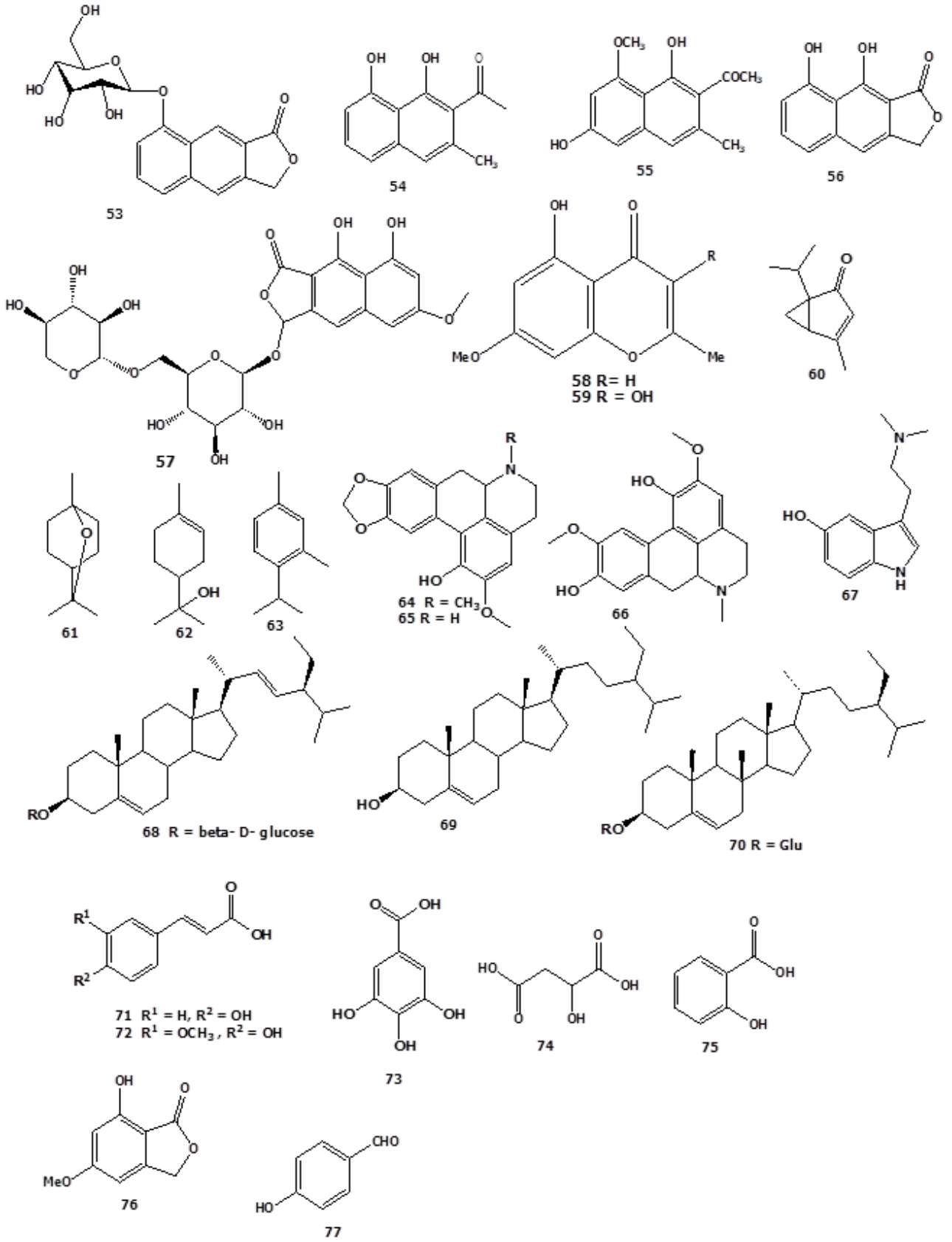

Figure 4 : Napthalenic derivatives, terpenoids, alkaloids, organic acids and other compounds reported from the *genus Rhamnus.*

Essential oils

The essential oils from plants are known with various pharmacological activities (112). Campbell et al., (2019) reported essential oils from the leaves of R. prinoides of which 4-hydroxy-4-methyl-2-pentanone and ethyl 4-ethoxybenzoate score more than 85% and exhibited significant anti-biofilm activity (113). In a related study, Chouitah et al., (2012) reported essential oils from the leaves of R.alaternus (114) of which camphene (17.63 %), linalool (16.13 %), pulegone (15.01 %), naphthalene (14.66 %), mequinol (2.77 %) and borneol (2.13 %) are among the major components.

Pharmacological activities

Hepatoprotective activity

Berroukche *et al*. (2015) evaluated hepatoprotective activity of the macerated *R. alaternus* extract in Wistar rats treated with the toxic carbon tetrachloride (CCl_4) that causes hepatic damage through evaluation of both the biochemical and histopathological changes in rats. The extracts with bodily weight (250 mg/kg) reduced the elevated levels of alkaline phosphatase (ALP),Glutamic oxaloacetic transaminase (GOT),Glutamic pyruvic transaminase (GPT) and total bilirubin and significantly attenuated the deleterious histopathologic changes in the liver after carbon tetrachloride (CCl_4)-intoxication (14).

Anti-inflammatory activity

Thakru and Prasad (2019) evaluated *in vivo* anti-inflammatory activity of ethanolic extract of *R.purpureus* stem bark using the carrageenan-induced rat paw edema assay in adult Swiss albino mice, where 200 mg/kg bodily weight of the extract was administered orally to different groups of mice with indomethacin (10mg/kg) as the positive control. The crude ethanolic extract showed considerable ($P < 0.05$) anti-inflammatory activity with inhibition of 54.50% and 54.77% after 3 h and 4 h of treatment as compared to the standard drug indomethacin (10 mg/kg) showed the inhibition of 50.46%, and 51.78% after 3 h and 4 h of treatment, respectively (115).

Chen *et al*., (2018) evaluated the anti-inflammatory activity of apigenin (**40**) and Kaempferol (**33**) isolated from 80% methanol bark extract of *R.davurica* Pall using the cyclooxygenase (COX-2) inhibition assay, with aspirin as the positive control. Apigenin (**40**) and Kaempferol (**33**) exhibited anti-inflammatory activity with IC_{50} values of 10.14 and 9.27 µg/mL, respectively (74). Chen *et al*., (2020) evaluated anti-inflammatory activity of 60% ethanol stem and stem bark semi-purified extracts of *R.prinoides* using cyclooxygenase (COX-2) inhibition assay, with aspirin as the positive control. The semi-purified extract exhibited activity with IC_{50} value of 20.6 µg/mL, which was weak activity compared to IC_{50} value of 6.33 µg/mL exhibited by ascorbic acid (116).

Antibacterial activity

Molla *et al*., (2016) evaluated antibacterial activities of methanol and chloroform solvent fractions of *R.prinoides* crude leaves extract against *S. aureus*, *S. pyogen*, *S. pneumoniae,* and *S. typhi* using agar well diffusion methods with ampicillin and ciprofloxacin as positive controls. Methanol and chloroform extracts revealed antibacterial activities at different concentrations (78 mg/well, 39 mg/well, and 19.5 mg/well). The average minimum inhibitory concentration of the methanol and chloroform extracts ranged from 8.13-32.5 mg/mL and 8.13-16.25 mg/mL, respectively (117).

Ammar *et al*., (2007) evaluated the antibacterial activities of petroleum ether, chloroform, ethyl acetate, methanol, and total Oligomers flavonoids (TOF) enriched leaves extracts of *R.alaternus* against *S. aureus*, *E. faecalis*, *E. coli*, *S. enteritidis and S. typhimurium* using micro dilution and agar dilution methods. The TOF extracts showed activities against *S. aureus*, *E. faecalis*, *E. coli*, *S. enteritidis* and *S. typhimurium* with MIC values of 120 µg/mL,175 µg/mL, 1.75 mg/mL, 125 µg/mL and 62.5 µg/mL, respectively, while the ethyl acetate extract exhibited with MIC values of 70 µg/mL, 150 µg/mL, 3.75 mg/mL, 100 µg/mL and 175 µg/mL, respectively (118).

Chouitah *et al*., (2012) evaluated antibacterial activities of essential oils of *R.alaternus* leaves against *P. aeroginosa*, *E. coli* and *S. typhimurium* using the paper disc diffusion method. The essential oils exhibited activities with zones of inhibition 8, 17 and 15 mm, respectively (114). Carranza *et al*., (2015) evaluated antibacterial activities of methanol extracts of leaves and bark of *R. californica* against *B. cereus*, *S. pyogenes*, *M. smegmatis*, *S. aureus*, *methicillin-resistant S. aureus* (*MRSA)*, *E. coli,* and *P. aeruginosa* using disc diffusion and minimal inhibitory concentration (MIC) assays. Both extracts inhibited MRSA growth and other Gram-positive bacteria with MICs of 3.3-6.0 mg/mL (77). Raja *et al*., (2018) evaluated antibacterial activities of ethyl acetate extract of *R.wightii* whole part against *S. aureus*, *B. cereus*, *E. faecalis*, *K. pneumonia*, *P. aeruginosa* and *E. coli* using agar disc diffusion method with streptomycin and gentamycin as positive controls. The ethyl acetate extract of the whole part of *R.wightii* revealed inhibition zones (in mm) of 15, 16.66, 15, 19, 10.66 and 12, respectively, which is highly comparable with the positive control, streptomycin (25 µg/disc) and gentamycin (50

µg/disc). The isolated compound musizen (**54**) and standard drugs have additionally inhibited *S. aureus* and *K. pneumonia* growth at a concentration (MIC value) of 9 µg/mL and 120 µg/mL, respectively (76).

Kosalec *et al*., (2013) evaluated antibacterial activities of methanol bark extracts of *R. alaternus*, *R. fallax*, *R. intermedia* and *R. pumila* against *S. aureus*, *P. aeruginosa* and *E. coli* using micro-dilution broth assay. All plant extracts exhibited activities with MIC values of ranging from 1.25 to 2.5 µg/mL (86). Carranza *et al*., (2015) evaluated antibacterial activities of methanol leaf extracts of *R.californica* against *S. aureus*, *Methicillin-resistant S. aureus*, *B. cereus*, *P. aeruginosa*, *S. pyogenes* and *E. coli* using Kirby-Bauer disc diffusion assay with streptomycin as positive control. The extract exhibited activities with zone of inhibition ranging from 9 mm to 14.3 mm, which was moderate activities compared to the standard with zone of inhibition ranging from 17 mm to 23.8 mm (77).

Antifungal Activity

Kosalec *et al*., (2013) evaluated antibacterial activities of methanol bark extracts of *R. alaternus*, *R. fallax*, *R. intermedia* and *R. pumila* against *C. albicans*, *A. niger* and *M. gypseum* using micro-dilution broth assay. All the plant extracts exhibited activities with MIC values of 0.625 mg/mL and 2.5 mg/mL against *Candida albicans* and *Aspergillus niger,* respectively, whereas extracts of *R. fallax*, *R. intermedia* and *R. pumila* exhibited with MIC value of 0.313 mg/mL against dermatophyte species (*Microsporum gypseum*) (86).

Antimalarial activity

Koch *et al*. (2009) evaluated antimalarial activities of chloroform root bark extracts of *R. prinoides* against chloroquine-sensitive *Plasmodium falciparum* strain using ELISA assay with chloroquine as standard drug. The extract exhibit with IC_{50} value of 3.53µg/mL, which was weak activities compared to IC_{50} value of 0.004 µg/mL exhibited by chloroquine the standard drug (119). Another study evaluated the anti-plasmodia activities of n-hexane, dichloromethane, and methanol root extracts of *R.prinoides* using the radioisotope method. All extracts were found to have *in vitro* antimalarial activity. The highest activity was displayed by n-hexane and dichloromethane extracts with IC_{50} values of 19.9 µg/mL and 30.3 µg/mL, respectively (120). The naphthalene derivative geshoidin (**53**) from *R.prinoides* showed an IC_{50} value of 4.0 pM and 0.4 pM against the chloroquine-sensitive (D6) and chloroquine-resistant (W2) strains of *Plasmodium falciparum* (121). In a related study, *in vivo* anti-malarial activity of aqueous extracts from leaves and root barks of *R.staddo*, *R. prinoides* and their chloroquine (CQ) potential effects against a blood-induced CQ-resistant rodent parasite in mice showed high chemo suppression in the range 51% -75% (122). Results of those studies suggest that the extracts of *R.prinoides* have a promising antiplasmodial activity which supports the folkloric use of the plant for treating malaria.

Antioxidant activity

Bhouri *et al*., (2011) evaluated Kaempferol 3-*O*-*β*-isorhamninoside (**31**) and rhamnocitrin 3-*O*-*β*-isorhamninoside (**36**) isolated from soxhlet methanolic leaves extract of *R.alaternus* using superoxide radical scavenging activity with riboflavin as reference signal. The compounds produced an 80.4% and 85.6% decrease in NBT/riboflavin photo reduction, respectively, at a dose of 150 µg/assay. However K3O-ir was more potent superoxide scavenger with an IC_{50} value of 18.75 µg/mL than R3O-ir (IC_{50} = 22.5 µg/mL)(73). Rocchetti *et al*., (2019) determined the antioxidant activities of methanol and aqueous unmature fruit extracts of *R.petiolaris* using radical scavenging activities (DPPH and ABTS assay) with reported as trolox equivalents (mgTE/g extract) as reference. The methanolic and aqueous unmature fruit extracts were the most effective 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) scavenger (470.96 mg trolox equivalent (TE)/g and 394.96 mg TE/g) respectively (123).

Zeouk *et al*., (2020) evaluated *in vivo* antioxidant activities of ethanolic extracts of *R.alaternus* leaves using scavenging activities (DPPH assay) with butylated hydroxytoluene (BHT) as a standard. The crude extract showed activities with IC_{50} value of 58 µg/mL, which has good antioxidant activities when compared to IC_{50} value of 31 µg/mL exhibited by butylated hydroxytoluene (BHT), the positive control. Similarly, ethanolic extracts of *R.alaternus* leaves fraction have exhibited highest antioxidant activity with IC_{50} values of 32.76%, 27.01% and 38.87%, respectively(96).

Ammar *et al*., (2008) evaluated the antioxidant activity of aqueous extract and ethyl acetate fraction leaves of *R.alaternus* using Xanthine Oxidase (XOD) assay with allopurinol as positive control. The aqueous extract and ethyl acetate fraction exhibited high xanthine oxidase inhibiting with respective IC_{50} values of 208 and 137 µg/mL and super oxide anion scavenging effects with IC_{50} values of 132 and 117 µg/mL (124). Ammar *et al*., (2009) evaluated the antioxidant activities of methanolic and total oligomer flavonoid enriched extracts from *R.alaternus* leaves using DPPH radical scavenging and xanthine oxidase (XOD) assay with vitamin E and allopurinol as positive control, respectively. Rhamnetin-3-O-

isorhamninoside (**37**) showed DPPH activities with IC_{50} value of 1.5 µg/mL which is more antioxidant activity as compared to IC_{50} value of 3 µg/mL exhibited by vitamin E the standard drug. Similarly, the isolated compound exhibited xanthine oxidase (XOD) inhibiting with respective IC_{50} values of 18, 81 and 40 µg/mL and superoxide anion scavenging effects with IC_{50} values of 42,79 and 35 µg/mL as compared with the positive control allopurinol having IC_{50} value of 37 and 4 µg/mL, respectively (72).

Ben Ammar *et al*., (2008) evaluated antioxidant activities of methanol extracts from *R.alaternus* leaves and root bark using DPPH radical scavenging and xanthine oxidase (XOD) assay with α–tocopherol and allopurinol as positive control, respectively. The root bark extract of *R.alaternus* revealed more effective than the leaves extract with IC_{50} values of 7.21 and 18.84 µg/mL, respectively, compared to IC_{50} value of 3 µg/mL exhibited by α-tocopherol. Similarly, the leaves and root bark extract exhibited xanthine oxidase (XOD) inhibiting with respective IC_{50} values of 103.96 and 83.33 µg/mL and superoxide anion scavenging effects with IC_{50} values of 171 and 92 µg/mL compared to allopurinol having IC_{50} value of 37.3 and 6 µg/mL, respectively(125).

Bhouri *et al*., (2012) evaluated antioxidant activities of Kaempferol-3-O-β-isorhamninoside and rhamnocitrin 3-O-β-isorhamninoside (**37**) isolated from leaves of *R. alaternus* using cupric reducing antioxidant capacity (CUPRAC), reducing power assay, and ferric reducing antioxidant power (FRAP) with Trolox (10-1000 µg/mL) as a positive control. The compound K3O-ir and R3O-ir exhibited a significant ability to reduce the Cu^{2+} neocuproine complex to Cu^{+} neocuproine in a dose dependent manner. The highest values obtained with 1 mg/mL of each compound, were 374 µg/mL and 310 µg/mL equivalent to Trolox, respectively. The reducing power assay evaluates antioxidant capacity of compounds based on their ability to reduce ferric (Fe^{3+}) to ferrous (Fe^{2+}) ion through the donation of an electron, with the resulting ferrous ion (Fe^{2+}) formation monitored spectrophotometrically at 700 nm. The tested compounds exhibited good reducing potential a concentration of 1 mg/mL. R3O-ir exhibited higher reducing power of iron (368 µg/mL equivalent of Trolox) than K3O-ir (330 µg/mL equivalent of Trolox) (126).

Chaouche *et al*., (2020) evaluated the antioxidant activities of methanol-acetone leaves and stem bark extracts of *R. alaternus* using DPPH radical scavenging and ferric reducing antioxidant potential (FRAP) assay with butylated hydroxyanisole (BHA) as a positive control. The leaves and stem bark extracts exhibited DPPH activities with IC_{50} values of 10.5 and 51.2 µg/mL, respectively, which was weak activity compared to IC_{50} value of 5.6 µg/mL exhibited by BHA the positive control. Similarly, the leaves and stem bark extracts exhibited FRAP activities with EC_{50} values of 0.4 and 1.8 µg/mL, respectively, which was weak activity compared to EC_{50} value of 0.1 µg/mL exhibited by BHA (127).

Hsiao *et al*., (1996) evaluated antioxidant activities of compound isotorachrysone (**55**) isolated from root bark extracts of *R.nakaharai* using iron-induced lipid peroxidation technique in rat brain homogenates with butylated hydroxytoluene (BHT), alpha tocopherol and desferrioxamine as a positive controls. The study revealed that isotorachrysone (**55**) exhibited IC_{50} value of 1.64 µM, which was comparable to IC_{50} value of 1.08µM exhibited by BHT and was more potent than alpha tocopherol and desferrioxamine with IC_{50} values of 3.71 and 97.10 µM as standard drug (111).

Kosalec *et al*., (2013) evaluated antioxidant activities of bark extracts of *R. alaternus*, *R. fallax*, *R. intermedia* and *R. pumila* using β-carotene-linoleic acid, DPPH radical scavenging, reducing power assay, and chelating activity with BHA, ascorbic acid, quercetin, and EDTA as positive controls. All the plant extracts, *R. alaternus*, *R. fallax*, *R. intermedia* and *R. pumila* exhibited activities using β-carotene-linoleic acid assay with EC_{50} values of 250, 289, 38 and 29.5 µg/mL respectively, which was greater activity compared to EC_{50} value of 852 µg/mL exhibited by ascorbic acid. Similarly, all the plant extracts, *R. alaternus*, *R. fallax*, *R. intermedia* and *R. pumila* exhibited activities using reducing power assay with EC_{50} values of 0.91, 1.99, 0.81 and 0.99 µg/mL respectively, which was comparable and greater activities compared to EC_{50} values of 7.53, 1.8 and 7.59 µg/mL, respectively, exhibited by BHA, quercetin and ascorbic acid as standard drugs (86).

Lu *et al*., (2016) evaluated antioxidant activates of alaternin (**10**) and emodin-8-O-glucoside (**20**) isolated from methanol extracts of *R.nakaharai* heart wood using ABTS, DPPH and Superoxide dismutase (SOD-like) assay with ascorbic acid, 3-t-butyl-4-hydroxynisode (BHA) as positive control. The compound alaternin (**10**), showed DPPH activity with IC_{50} value of 117.7 µM, which was moderate activities compared to IC_{50} value of 63.7 µM exhibited by ascorbic acid. Also, alaternin (**10**) and emodin-8-O-glucoside (**20**) exhibited SOD-like activities with IC_{50} values of 247 and 232 µM, respectively, which were better activities compared to IC_{50} value of 292 µM exhibited by BHA (70). Chen *et al*., (2020) evaluated antioxidant activities of 60% ethanol stem and stem bark crude and semi purified extracts of *R.prinoides* using DPPH

and ABTS assay with butylated hydroxytoluene (BHT) as positive control. The semi-purified extract exhibit DPPH activities with IC_{50} value of 0.2 mg/mL, which was more potent than the standard BHT having IC_{50} value of 0.286 mg/mL. Similarly, the crude extracts exhibit ABTS activities with IC_{50} value of 0.0596 mg/mL, which was comparable to IC_{50} value of BHT (116).

Mazhar *et al*., (2013) evaluated antioxidant activities of methanol extract and their fractions (ethyl acetate, n-butanol, chloroform and n-hexane) of *R.triquetra* aerial parts using DPPH assay with butylated hydroxytoluene (BHT) as a positive control. The crude extract and their fractions exhibited activities with IC_{50} values of 70.26, 7.59, 37.98, 60.09 and 182.99 µg/mL respectively, of which the ethyl acetate fraction showed better activity among the extracts, compared to IC_{50} value of 12.1 µg/mL exhibited by BHT (128). Boussahel *et al*., (2013) evaluated antioxidant activities of methanol and aqueous extract of *R. alaternus* leaves using DPPH and β-carotene-linoleic acid assay with butylated hydroxytoluene (BHT) as a positive control. The methanolic and aqueous extracts exhibited DPPH activities with IC_{50} values of 0.082 and 0.398 mg/mL, respectively, of which methanol extract is more active, compared to IC_{50} value of 0.032 mg/mL exhibited by BHT. Similarly, the methanol extract exhibited activities using β-carotene-linoleic acid assay with 89% inhibition, which was comparable to 99.2% inhibition displayed by BHT (129). Boussahel *et al*., (2015) evaluated antioxidant activities of methanol bark extract of *R. alaternus* using oxygen radical absorbance capacity assay (ORAC) with trolox equivalent antioxidant capacity as a standard. The extract exhibited with 6.55 mmol TE/g extract, which was more active as compared to the standard TEAC with 0.75 mmol TE/g extract (130).

Antiproliferative Activity

Ben Ammar *et al*., (2008) evaluated the antiproliferative effect of root bark and leaves extracts obtained from *R. alaternus* against K562 human cell line and L1210 mouse lymphoma cells, at various concentrations comprised between 100 and 800 µg/mL using tetrazolium salt (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) (MTT) assay. The leaves and roots extracts from *R. alaternus* showed interesting antiproliferative in a dose-dependent manner. The root extract was more effective than the leaves, on both types of leukemia cells. Indeed, concerning the K562 human cell, the IC_{50} values of roots and leaves extracts were determined at 165 and 260.69 µg/mL, respectively. Concerning the L1210 cells, the IC_{50} values of roots and leaves extracts were determined at 210.73 and 343.10 µg/mL, respectively, in the presence of α-tocopherol as positive control (125).

Chen *et al*., (2016) evaluated the antiproliferative effect of 80% methanol extracts obtained from *R.davurica* using protein-staining sulforhodamine B (SRB) microculture colorimetric assay against human cancer cell lines of HT-29 (intestinal carcinoma) and SGC-7901 (gastric carcinoma). The extract exhibited significant dose-dependent antiproliferative activities against HT-29 and SGC-7901 cells with IC_{50} values of 24.96 and 89.53 µg/mL, respectively. Meanwhile, inhibitory activities against both HT-29 and SGC-7901 cells significantly increased by the treatment with *R. davurica* bark extract in a time-dependent manner from 24-96 h at a dose of 150 µg/mL, although there was a decrease on SGC-7901 cells at the time from 72 h–96 h (84).

Chen *et al*., (2018) evaluated the antiproliferative effect of compounds apigenin (**40**) and kaempferol (**33**) obtained from 80% methanol extracts of *R.davurica* bark using MTT colorimetric assay against three human cancer cell lines of Hep G2 (hepatic cancer), SGC-7901 (gastric carcinoma), and HT-29 (intestinal carcinoma). Kaempferol (**33**) exhibited antiproliferative activities against HT-29, SGC-7901 and Hep G2 cells with IC_{50}values of 25.7, 13.43 and 20 µg/mL respectively, while the compound apigenin (**40**) exhibited with IC_{50} values 19.79, 17.76 and 10.20 µg/mL, respectively (74).

Wound healing Activity

Tessema *et al*., (2021) evaluated wound healing activities of methanol leaf extracts of *R.prinoides* using excision and incision models in adult Swiss albino mice, with nitrofurazone ointment as a standard. Treatment with 5 % and 10 % (w/w) methanol extract ointment exhibited significant wound recovery activities in both excision and incision models, which has higher activity when compared the standard nitrofurazone ointment (131).

Cytotoxicity and Toxicity Activity

Ahmadi *et al*., (2016) evaluated the cytotoxic activities of hydroalcoholic extracts of *R.frangula* against breast cancer cellline (MCF-7) using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay. The extract exhibited activities with half maximal cytotoxic concentration (CC_{50}) value of 10 mg/mL (132). Ben Ammar *et al*., (2008) evaluated the cytotoxic activities of petroleum ether, chloroform, ethyl acetate, methanol and total oligomers flavonoids (TOF) enriched leaves extracts of *R.alaternus* against human chronic myelogenous K562 and murine Leukaemia L1210 cells using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The TOF extract exhibited

with IC_{50} values of 75 µg/mL and 198 µg/mL against K562 and L1210 cells, respectively. Similarly, the ethyl acetate extract showed activities with IC_{50} values of 232 µg/mL and 176 µg/mL respectively (125).

Bhouri *et al*., (2011) evaluated the cytotoxic activities of kaempferol 3-O-β-isorhamninoside and rhamnocitrin 3-O-β-isorhamninoside isolated from methanol leaves extracts of *R.alaternus* using Alamar blue assay against human lymphoblastoid TK6 cells, with cells treated by 0.5% DMSO as a control. The compound neither K3O-ir nor R3O-ir reached 50% inhibition of TK6 cell proliferation (75). Chen *et al*., (2016) evaluated *in vitro* toxicity activity of 80% ethanol bark extracts of *R. davurica* against normal human hepatic cells (L-O2) using protein-staining sulforhodamine B (SRB) microculture colorimetric assay. The extract exhibited activities with IC_{50} value of 229.19 µg/mL on L-O2, which suggested that *R. davurica* bark extract showed very low or no toxicity on hepatic cell viability (84).

Mai *et al*., (2001) evaluated cytotoxicity activity of prinoidin (**23**) isolated from methanol extracts of *R.nepalensis* fruit against KB (human epidermoid carcinoma of the mouth) cell using MTT assay with doxorubicin as a positive control. Prinoidin (**23**) exhibited IC_{50} value of 0.045 µM, which was four times more potent than the standard, doxorubicin, having IC_{50} value of 0.2 µM (69). Boussahel *et al*., (2015) evaluated cytotoxicity of methanol extract of *R.alaternus* bark against human monocytic leukemia cells (U937) using trypan blue assay with taxol as standard drug. The extract exhibited activities with IC_{50} values of 6.39 µg/mL, which was comparable to IC_{50} value of 2.47 µg/mL exhibited by taxol the standard drug (130).

Anti-tyrosinase Activity

Lu *et al*., (2016) evaluated the anti-tyrosinase activity of 6-methoxysorigenin (**12**) isolated from methanol extracts of *R.nakaharai* using mushroom tyrosine inhibitory assay with kojic acid as positive control. The study revealed that 6-methoxysorigenin (**12**) exhibited activities with IC_{50} value of 42.2 µM, which was twofold inhibitory effect than the positive control kojil acid having IC_{50} value of 82.1 µM (70).

Antihyperlipidemic Activity

Tacherfiout *et al*., (2018) evaluated antihyperlipidemic activities of methanol extracts of *R.alaternus* leaf on circulating lipids in rats with Triton WR-1339-induced hyperlipidemia, intracellular lipid accumulation and expression of genes of fatty acid metabolism in human hepatoma HepG2 cells, and adipogenesis in the 3T3-L1 murine adipocyte cell model. The Oral crude extract administration decreased blood levels of cholesterol and triacylglycerol in hyperlipidemic rats (by 60% and 70%, respectively, at 200 mg extract/kg). In HepG2 cells, the extract exposure dose-dependently decreased intracellular lipids and up-regulated gene expression of carnitine palmitoyl transferase 1 involved in fatty acid oxidation, while in the 3T3-L1 model the extract favored preadipocyte proliferation and adipogenesis, pointing to positive effects on adipose tissue expandability(133).

Ammar *et al*., (2009) evaluated the anti lipid peroxidation activity of kaempferol 3-O-β-isorhamninoside, rhamnocitrin-3-O-isorhamninoside and rhamnetin-3-O-β-isorhamninoside (**37**) from methanol leaf extracts of *R. alaternus*was estimated by calculating the values of malondialdehyde (MDA) in cultured K562 human chronic myelogenous leukemia cells. In this study, the compounds displayed IC_{50} values of 180,320 and 106 µg/mL, respectively, compared to IC_{50} value of 15µg/mL exhibited by vitamin C as a reference (72).

Antimutagenic activity

Ammar *et al*., (2008) evaluated the antimutagenic activity of leaves extracts by the Ames assay, using the mutagen Aflatoxin B1 (AFB1) at a concentration of 10 µg/mL. The experiment was carried out with two strains of *Salmonella Typhimurium* (i.e., TA98 and TA100) in the presence of various extracts, and spontaneous revertant was used as control. Petroleum ether, chloroform, methanol, water, and total oligomers flavonoids (TOF) extracts obtained by *R. alaternus* were investigated at various doses (10, 50, and 250 µg/mL) and remarkably reduced the AFB1-induced mutagenicity. The study revealed that ethyl acetate extract to be the most effective at a dose of 250 µg/mL. At such dose, the inhibition percentage of mutagenicity was determined by the Ames assay up to 78% for the TA98 strain (124).

Antigenotoxic activity

Bhouri*et al*., (2011) evaluated the antigenotoxic activity of Kaempferol 3-O-β-isorhamninoside and rhamnocitrin3-O-β-isorhamninoside isolated from methanol extract of leaves of *R. alaternus* on *E. coli* PQ37 using SOS chromo test with two positive control snifuroxazide and aflatoxin B1 used at 10 µg/assay and 5 µg/assay, respectively. The assay carried out in absence of both aflatoxin B1 and extracts constituted the negative control. For the three flavonoid concentrations studied (1, 5, and 10 µg/assay), the antigenotoxic activity of rhamnocitrin 3-O-β-isorhamninoside was higher than the one determined for Kaempferol 3-O-β-isorhamninoside (73).

Bhouri *et al*., (2012) evaluated antigenotoxic properties of Kaempferol 3-O-β-isorhamninoside

(**31**) and rhamnocitrin 3-O-β-isorhamninoside (**36**) isolated from leaves of *R. alaternus* (i.e.,) using comet assay on human lymphoblastoid cells TK6 and NH32. Quantification of the comet data was reported as Total DNA damage (TDD). The compound exhibited no significant difference was detected between the TDD induced by K3O-ir (TDD=212, 151 and 67 at concentrations of respectively of 800, 400 and 200 µg/mL) and that induced by R3O-ir (TDD=238, 139 and 110) at the same tested concentrations in TK6 cells and the negative control (non-treated cells; TDD=163) on the other hand. In the opposite, a significant increase of the total DNA damage (TDD=348) was observed in TK6 cells exposed to 75 µM of H_2O_2, compared to the untreated cells. Likewise, K3O-ir and R3O-ir revealed a non genotoxic effect at the doses of (200 and 400 µg/ml) whereas the highest tested concentration (800 µg/mL) exhibited a genotoxic effect when tested with NH32 cells. The TDD values were 240 and 226 with respectively K3O-ir and R3O-ir, suggesting inducing of DNA breakage in p53 deficient lymphoblastoid human cells (126).

Summary of pharmacological activity of *Rhamanus* species is presented in Table 3 below.

Table 3: Pharmacological activities of extracts and isolated compounds from *Rhamnus* species

Activity	Plant species	Extract	Plant Part	Method	Effect	Refs
Hepatoprotective	*R. alaternus*	aqueous	leaves	Biochemical and histopathological changes in Wistar rats	Extract reduced levels of alkaline phosphatase (ALP), Glutamic oxaloacetic transaminase (GOT), Glutamic pyruvic transaminase (GPT) and total bilirubin and significantly attenuated deleterious histopathological changes in the liver	(14)
Anti-inflammatory	*R. alaternus*	ethanol	Stem bark	Carrageenan-induced rat paw edema assay	extract exhibited anti-inflammatory activity with inhibition of 54.50% and 54.77% after 3 hr and 4 hr of treatment as compared the standard drug indomethacin (10 mg/kg) showed the inhibition of 50.46%, and 51.78% after 3hr and 4hr of treatment, respectively	(115)
Anti-inflammatory	*R. prinoides*	ethanol	Stem and stem bark	Cyclooxygenase (COX-2) assay	extract exhibited activities with IC_{50} value of 20.6 µg/mL, which was weak activities compared to IC_{50} value of 6.33 µg/mL exhibited by ascorbic acid the standard	(116)
Anti-inflammatory	*R. davurica*	methanol	bark	Cyclooxygenase (COX-2) assay	The isolated compounds, apigenin (**40**) and Kaempferol (**33**) exhibited activities with IC_{50} values of 10.14 and 9.27 µg/mL respectively	(74)
Antibacterial	*R. prinoides*	Methanol and chloroform	leaves	Agar well diffusion	Extract exhibited activities against *S. aureus*, *S. pyogen*, *S. pneumoniae,* and *S. typhi* with MIC value of methanol and chloroform fractions ranged from 8.13 mg/mL to 32.5 mg/mL and from 8.13 mg/mL to 16.25 mg/mL, respectively.	(117)
Antibacterial	*R. californica*	methanol	Leaf and bark	Disc diffusion	Both extracts exhibited activities against *B. cereus*, *S. pyogenes*, *M. smegmatis*, *S. aureus*, *methicillin-resistant S. aureus (MRSA*) with MIC value of 3.3-6.0 mg/mL	(77)
Antibacterial	*R. alaterus*	Ethyl acetate and Total Oligomers flavonoids (TOF)	leaves	Microdilution and agar dilution	The TOF extract exhibited activities against *S. aureus*, *E. faecalis*, *E. coli*, *S. enteritidis and S. typhimurium* with MIC values of 120 µg/mL,175 µg/mL, 1.75 mg/mL, 125 µg/mL and 62.5 µg/mL respectively, while the ethyl acetate extract exhibited with MIC values of 70µg/mL, 150µg/mL, 3.75 mg/mL, 100 µg/mL and 175 µg/mL respectively	(118)
Antibacterial	*R. wightii*	Ethyl acetate	Whole part	Agar disc diffusion	Extract exhibited activities against *S. aureus*, *B. cereus*, *E. faecalis*, *K.pneumonia*, *P. aeruginosa* and *E. coli*with inhibition zones (in mm) of 15, 16.66, 15, 19, 10.66 and 12 respectively	(76)
Antibacterial	*R.*	methanol	Bark	Micro-dilution	All extract exhibited activities against *S. aureus*,*P.*	(86)

	alaternus,*R. fallax*,*R. intermedia* and *R. pumila*			broth assay	*aeruginosa* and *E. coli* with MIC value of ranging from 1.25 to 2.5 µg/mL	
Antibacterial	*R. californica*	methanol	Leaves	Kirby-Bauer disc diffusion	Extract exhibited activities against *Staphylococcus aureus*, *Methicillin-resistant Staphylococcusaureus*, *Bacillus cereus*,*Pseudomonas aeruginosa*,*Streptococcus pyogenes* and *Escherichia coli*with zone of inhibition ranging from 9 mm to 14.3 mm	(77)
Antibacterial	*R. wightii*	Ethyl acetate	Whole part	Agar disc diffusion	Musizen (**54**) exhibited activities against *S. aureus* and *K. pneumonia* with MIC value of 9 µg/mL, which was more potent than the standard drug Streptomycin having MIC value of 120 µg/mL	(76)
Antifungal	*R. alaternus*, *R. fallax*,*R. intermedia* and *R. pumila*	methanol	Bark	micro-dilution broth assay	All extract exhibited activities against *C. albicans*, *A. niger* and *M.gypseum* with MIC values of 0.625 mg/mL and 2.5 mg/mL against *C. albicans* and *A.niger* respectively, while the plant extracts *R. fallax*,*R. intermedia* and *R. pumila* exhibited with MIC value of 0.313 mg/ml against dermatophyte species (*M. gypseum*)	(86)
Antimalarial	*R. prinoides*	Chloroform	Root bark	ELISA assay	extract exhibited activities against chloroquine-sensitive *Plasmodium falciparum* strain with IC_{50} value of 3.53 µg/mL, which was weak activities compared to IC_{50} value of 0.004 µg/mL exhibited by chloroquine the standard drug	(119)
Antimalarial	*R. prinoides*	Hexane& dichloromethane	root	Radioisotope	extracts of hexane and dichloromethane exhibited activities anti-plasmodia with IC_{50} values of 19.9 µg/mL and 30.3 µg/mL, respectively	(120)
Antimalarial	*R. prinoides and R. staddo*	aqueous	Leaves and root bark	blood-induced CQ-resistant rodent parasite in mice	The plant extract and standard drug,chloroquine (CQ) potential effects against a blood-induced CQ-resistant rodent parasite in mice showed high chemo suppression in the range 51% -75%	(122)
Antioxidant	*R. alaterus*	methanol	Root bark and leaves	DPPH , Xanthine Oxidase (XOD) and Superoxide anion scavenging effects	The root bark and Leaves extract exhibited DPPH activities with IC_{50} values of 7.21 and 18.84 µg/mL, respectively, when compared to IC_{50} value of 3 µg/mL exhibited by α-tocopherol the positive control. Similarly, the leaves and root bark extract exhibited xanthine oxidase (XOD) inhibiting with respective IC_{50} values of 103.96 and 83.33 µg/mL and superoxide anion scavenging effects with IC_{50} values of 171 and 92 µg/mL as compared with the positive control allopurinol having	(125)

					IC50 value of 37.3 and 6 µg/mL respectively	
Antioxidant	*R. petiolaris*	Methanol and aqueous	fruit	DPPH and ABTS assay	Extracts exhibited activities with 470.96 mg trolox equivalent (TE)/g and 394.96 mg TE/g) respectively	(123)
Antioxidant	*R. alaternus*	methanol	leaves	DPPH, Xanthine Oxidase and Superoxide anion scavenging effects	Rhamnetin-3-O-β-isorhamninoside (**38**) exhibited DPPH activities with IC_{50} value of 1.5 µg/mL which is more antioxidant activity as compared to IC_{50} value of 3 µg/mL exhibited by vitamin E the standard drug. Similarly, kaempferol 3-O-β-isorhamninoside (**31**), rhamnocitrin-3-O-β-isorhamninoside (**36**) and rhamnetin-3-O-isorhamninoside (**37**) exhibited xanthine oxidase (XOD) inhibiting with respective IC_{50} values of 18, 81 and 40 µg/mL and superoxide anion scavenging effects with IC_{50} values of 42, 79 and 35µg/mL as compared with the positive control allopurinol having IC_{50} value of 37 and 4µg/mL respectively	(72)
Antioxidant	*R, alaternus*	methanol	leaf	Super oxide radical scavenging	Kaempferol 3-O-β-isorhamninoside (**31**) and rhamnocitrin 3-O-β-isorhamninoside exhibited activities with IC_{50} values 18.75 and 22.5 µg/mL respectively	(73)
Antioxidant	*R. nakaharai*	methanol	Heart wood	DPPH assay	The isolated compound, alaternin (**10**) exhibited activities with IC_{50} value of 117.7 µM, which was moderate activities compared to IC_{50} value of 63.7 µM exhibited by ascorbic acid the standard drug	(70)
Antioxidant	*R. nakaharai*		Root bark	Iron induced lipid peroxidation	The isolated compound, isotorachrysone (**55**) exhibited activities with IC_{50} value of 1.64 µM, which was comparable to IC_{50} value of 1.08 µM exhibited by the standard butylated hydroxyl toluene (BHT) and was more potent than α- tocophenol and desferrioxamine with IC_{50} values of 3.71 and 97.10 µM respectively	(111)
Antioxidant	*R. alaternus*	ethanol	leaves	DPPH assay	extract exhibited activities with IC_{50} value of 58 µg/mL, which has good antioxidant activities when compared to IC_{50} value of 31 µg/mL exhibited by butylatedhydroxytoluene (BHT), the positive control	(96)
Antioxidant	*R. alaterus*	Aqueous and ethyl acetate fraction	leaves	Xanthine Oxidase (XOD) and Super oxide anion scavenging	aqueous extract and ethyl acetate fraction exhibited high xanthine oxidase inhibiting with respective IC_{50} values of 208 and 137µg/mL, and super oxide anion scavenging effects with IC_{50} values of 132 and 117µg/mL	(124)
Antioxidant	*R. alaterus*	Methanol-acetone	Leaf and stem bark	DPPH assay and ferric reducing antioxidant potential	leaves and stem bark extracts exhibited DPPH activities with IC_{50} values of 10.5 and 51.2µg/mL respectively, which was weak activity compared to IC_{50} value of 5.6µg/mL exhibited by BHA the positive control and FRAP	(127)

					activities with EC_{50} values of 0.4 and 1.8 µg/mL respectively, which was weak activity compared to EC_{50} value of 0.1 µg/mL exhibited by BHA the positive control	
Antioxidant	*R. alaternus*		leaves	Cupric reducing antioxidant (CUPRAC), reducing power assay and ferric reducing antioxidant power (FRAP)	Kaempferol 3-O-β-isorhamninoside (**31**) and rhamnocitrin 3-O-β-isorhamninoside (**36**) exhibited CUPRAC and reduced power assay activities with IC_{50} value of 1 mg/mL, while FRAP activities exhibited at the same concentration 1000 µg/mL reduce a maximum of iron ion by 300 µg/mL and 320 µg/mL equivalent of Trolox respectively	(126)
Antioxidant	*R. alaternus, R. Fallax, R. intermedia and R. pumila*		Bark	beta-Carotene-linoleic acid, DPPH radical scavenging, reducing power assay and Chelating activity	All exhibited activities using β-Carotene-linoleic acid assay with EC_{50} values of 250,289, 38 and 29.5 µg.mL respectively, which was greater activity compared to EC_{50} value of 852 µg/mL exhibited by ascorbic acid the positive control. Similarly, all the plant extracts exhibited activities using reducing power assay with EC_{50} values of 0.91, 1.99, 0.81 and 0.99 µg/mL respectively, which was comparable and greater activities compared to EC_{50} values of 7.53, 1.8 and 7.59 µg/mL respectively exhibited by BHA, quercetin and ascorbic acid as standard drugs	(86)
Antioxidant	*R. prinoides*	ethanol	Stem and stem bark	DPPH and ABTS assay	The semi purified extract exhibited DPPH activities with IC_{50} value of 0.2 mg/mL, which was more potent than the standard BHT having IC_{50} value of 0.286 mg/mL. Similarly, the crude extracts exhibit ABTS activities with IC_{50} value of 0.0596 mg/mL, which was comparable to IC_{50} value of BHT, the positive control	(116)
Antioxidant	*R. triquetra*	methanol	Aerial part	DPPH assay	crude extract and their fractions (ethyl acetate , n-butanol, chloroform and n-hexane) exhibited activities with IC_{50} values of 70.26, 7.59, 37.98, 60.09 and 182.99 µg/mL respectively, which was the ethyl acetate fraction, is more active compared to IC_{50} value of 12.1 µg/mL exhibited by the standard (BHT)	(128)
Antioxidant	*R. alaternus*	Methanol and aqueous	leaves	DPPH and β-carotene-linoleic acid assay	The methanol and aqueous extracts exhibited DPPH activities with IC_{50} values of 0.082 and 0.398 mg/mL respectively, which was the methanol extract, is more active compared to IC_{50} value of 0.032 mg/mL exhibited by the standard (BHT). Similarly, the methanol extract exhibit activities using β-carotene-linoleic acid assay with 89% inhibition, which was comparable to 99.2% inhibition by BHT the standard	(129)

Antioxidant	*R. alaternus*	methanol	leaves	Oxygen radical absorbance capacity assay (ORAC)	extract exhibited with 6.55 mmol TE/g extract, which was more active as compared to the standard TEAC with 0.75 mmol TE/g extract	(130)
Anti-hyperlipidemia	*R. alaternus*	methanol	leaves	Calculating Malondialdehyde in cultured K562 cells	kaempferol 3-O-β-isorhamninoside (**31**), rhamnocitrin-3-O-β-isorhamninoside (**36**) and rhamnetin-3-O-isorhamninoside (**37**) from methanol leaf extracts exhibited by calculating the values of malondialdehyde (MDA) in cultured K562 human chronic myelogenous leukemia cells with IC_{50} values of isolated compound 180,320 and 106 µg/mL, respectively	(72)
Anti-hyperlipidemia	*R. alaternus*	methanol	leaves	Using Hyperlipidemia rats	The Oral crude extract administration decreased blood levels of cholesterol and triacylglycerols in human hepatoma HePG2 and 3T3-L1 murine dipocyte cell hyperlipidemic rats model (by 60% and 70%, respectively, at 200 mg extract/kg)	(133)
Anti-proliferative	*R. alaternus*	methanol	Root bark and leaf	MTT assay	The root barks and leaf extract exhibited activities against K562 cells with IC_{50} value of 165 and 260.69 µg/mL. Similarly the extracts exhibited activities against L1210 cells with IC_{50} value of 210.73 and 343.10 µg/mL, respectively	(125)
Anti-proliferative	*R. davurica*	methanol	bark	sulforhodamine B (SRB)micro culture colorimetric assay	The extract exhibited activities against human cancer cell lines HT-29 and SGC-7901 with IC_{50} values of 24.96 and 89.53 µg/mL. respectively	(84)
Anti-proliferative	*R. davurica*	methanol	bark	MTT colorimetric assay	Kaempferol (**33**) exhibited activities against human cancer cell lines HT-29, SGC-7901 and HePG2 with IC50 values of 25.7, 13.43 and 20 µg/mL respectively, while the compound apigenin (**40**) exhibited with IC50 values 19.79, 17.76 and 10.20 µg/mL respectively	(74)
Wound healing	*R. prinoides*	methanol	leaves	Excision and incision models in adult Swiss albino mice	Treatment with 5 % and 10 % (w/w) methanol extract ointment exhibited significant wound recovery activities in both excision and incision models	(131)
Cytotoxicity	*R. frangula*	hydroalcoholic		MTT assay	Extract exhibited activities against breast cancer cell lines (MCF-7) with half maximal cytotoxic concentration (CC_{50}) value of 10 mg/mL.	(132)
Cytotoxicity	*R. alaternus*	Ethyl acetate and Total Oligomers	leaf	MTT assay	TOF extract exhibited activities against human chronic myelogenous K562 and murine leukemia L1210 with IC_{50} values of 75 µg/mL and 198 µg/mL against K562 and L1210 cells respectively. Similarly, the ethyl acetate	(125)

		flavonoids			extract showed activities with IC_{50} values of 232 µg/mL and 176 µg/mL respectively	
Toxicity	*R. davurica*	ethanol	bark	Sulforhodamine B (SRB) microculture colorimetric assay	Extract exhibited activities against normal human hepatic cells (L-02) with IC_{50} value of 229.19 µg/mL .	(84)
Cytotoxicity	*R. alaternus*	methanol	leaf	Alamar blue assay	kaempferol 3-O-β-isorhamninoside (**31**) and rhamnocitrin 3-O-β-isorhamninoside (**36**) exhibited activities against human lymphoblastoid TK6 cells, the compound neither K3O-ir nor R3O-ir reached 50% inhibition of TK6 cell proliferation	(75)
Cytotoxicity	*R. nepalensis*	methanol	fruit	MTT assay	The isolated compound, prinoidin (**23**) exhibited activities against KB (human epidermoid carcinoma of the mouth) with IC_{50} value of 0.045 µM, which was four times more potent than the standard, doxorubicin having IC_{50} value of 0.2 µM	(69)
Cytotoxicity	*R. alaternus*	methanol	bark	Trypan blue assay	extract exhibited activities against human monocytic leukemia cells (U937) with IC_{50} values of 6.39 µg/mL, which was comparable to IC_{50} value of 2.47 µg/mL exhibited by taxol the standard drug	(130)
Anti-tyrosinase	*R. nakaharai*	methanol	Heart wood	Mushroom tyrosine inhibitory assay	6-methoxysorigenin (**12**) exhibited activities with IC_{50} value of 42.2 µM, which was twofold inhibitory effect than the positive control kojil acid having IC_{50} value of 82.1 µM	(70)
Anti-mutagenicity	*R. alaternus*	aqueous	leaf	Ames assay	The ethyl acetate fraction exhibited against *Salmonella Typhimurium* (TA98) strains with a dose of 250 µg/mL and 78% inhibition mutagenicity	(124)
Antigenotoxic	*R. alaternus*	methanol	leaf	SOS chromo test	kaempferol 3-O-β-isorhamninoside (**31**) and rhamnocitrin 3-O-β-isorhamninoside (**36**) on *E. coli* PQ37 at different concentration (1,5 and 10 µg/mL) showed antigenotoxicity activities	(73)
Antigenotoxic	*R. alaternus*	methanol	leaf	Comet assay	Kaempferol 3-O-β-isorhamninoside (**31**) and rhamnocitrin 3-O-β-isorhamninoside (**36**) exhibited activities against human lymphoblastoid cells TK6 at the same tested concentration, the total DNA damage induced by K3O-ir and R3O-ir showed no significant difference was detected	(126)

CONCLUSION

Traditional medicine continues as an alternative care available for the majority of the developing countries due to its intrinsic qualities, unique and holistic approaches as well as its accessibility and affordability. The present review endeavors to provide a comprehensive and up to date compilation of documented traditional medicinal uses, phytochemicals and pharmacological activities of the genus and provided valuable information in support of its uses as an alternative medicine for future healthcare practice. Phytochemicals including anthraquinones and flavonoids are the most dominant compounds reported from the genus of which polyphenols were abundant with tremendous antioxidant, wound healing and antiinflammatory activities. The genus afforded exemplary drug leads such as 6-methoxysorigenin (**12**) and prinoidin (**23**) with anti-tyrosinase and cytotoxicity as well as antioxidant drug leads such as Rhamnetin-3-*O*-*β*-isorhamninoside (**37**) and isotorachrysone (**55**). Nevertheless, more attention should be paid to the genus considering its wide spectrum of pharmacological properties. Further investigation should be conducted to evaluate promising cruds extracts as well as compounds in search for new drug candidates.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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