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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 *Rham*

Scientific name	Part	Distribution	Traditional use
R. alaternus L.	Leaf, Aerial Part,	Algeria	as a digestive, diuretic, laxative, ar hepatic and dermatological disorders
	Leaf	Algeria	treatment of gastrointestinal system di
	Bark	Algeria	Used to treat jaundice
	Aerial part	Algeria	Hepatic jaundice and chlorosis
	Root, Aerial Part	Spain, Iberian Peninsula	Used to treat depurative (blood purifica
	Aerial Part	Spain	therapeutics of hypercholesterolemia
	Aerial Part	Spain	therapeutics of antihypertensive (lower
	Bark, Branch	Italy	to treat hemostatic, wounds, laxative
	Branch, leaf	Iberian Peninsula	to treat high blood pressure
	Branch, Leaf	Israel, Algeria	to treat jaundice
R. alnifolia L'Hér	Root, Bark	USA	to treat gonorrhea and cathartic
R. alpina L.	Branch	Italy	to treat cardiac disease, wounds
R. cathartica L.	Bark	Bosnia and Herzegovina, Turkey	treatments of common buckthorn, diar
	Fruit	Southeast Europe	antiseptic for wounds
	Fruit	Serbia	to treat laxative
R. fallax L.	Bark	Bosnia and Herzegovina	to treat and manage dermal diseases
	Bark	Montenegro/ Serbia	to treat constipation
R. heterophylla Oliver	Root, Leaf	China	to cease bleeding
R. ilicifolia Kellogg	Root	USA	laxative, diuretic and to treat gonorrhe
	Whole Part	USA	analgesic or antirheumatic
R. lycioides L.	Leaves, Shoot	Turkey	to treat pulmonary cancer
R. nepalensis Wall MA Lawson	Root	India	to treat the treatment of pneumonia
R. nitudus Davis	Bark	Turkey	Used as emetic
R. persica Boiss.	Leaf	Iran	to treat allergy and itching in children,
R. prinoides L'Hér	Bark, Fruit, Multiple Part	Kenya	to treat sexually transmitted disease (g
	Fruit, Stem, Root, and Leaf	Kenya	to treat gonorrhea, prostate, malaria, b
	Root	Kenya	to treat muscular skeleton disord rheumatic)
	Leaf	Ethiopia	to treat Snakebite
	Roots, Leaf	South Africa	Used for blood purifiers, pneumonia,

			stimulants
	Branch	South Africa	Herpes, diabetes, HIV related infections
	Root, Leaf, and Steam	Kenya	to treat ear, nose, and throat (ENT) dis
	Leaf	Ethiopia, Uganda	to treat tonsillitis, wound, eczema, skin tuberculosis, dandruff, water-borne dis
	Seed	Ethiopia	to treat ringworm
	Root	Kenya	to treat sexually transmitted infection
	Root	Kenya	amoebiasis, bacillary dysentery, tonic,
	Root	Ethiopia	to treat hepatic problems
R. purpureus Edgew.	Bark, Steam, Fruit, Leaf	Himalayas	to treat digestive disorders
R. purshiana DC.	Bark	Algeria	to treat respiratory tract diseases (pha
	shell	Mexico	to treat skin rash and stomachache
R. staddo A.Rich	Tree	Kenya	Used for strength/nutrient supplem diseases, flu/cold
	Multiple Part	Kenya	to treat diarrhea
	Root, Steam,	Kenya	to treat gonorrhea, diabetes, endometr
R. triqueter Wall M. A. Lawson	Leaf, Fruit, Branch	Pakistan	to treat hemorrhagic septicemia
	Bark, Fruit	Himalaya	used for blood purifier, boils, scabies, s
R. virgatus Roxb.	Bark	Himalaya, India	to treat eczema and ringworms
	Steam, Fruit, Bark	Himalaya	to treat emetic, purgative, eczema, ring
	Fruit and Bark	Nepal/Iran	to treat diarrhea and dysentry
	Fruit, Bark	India	to treat emetic, spleen infection, and p of eyes

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
Anthraquinones		
Chryisophanol (**1**)	*R.formosana* and *R. serrata*	Root
	R.prinoides	Leaves, Stem
	R.alaternus	Stem, bark
	R.frangula	Stem bark and branch
	R.sphaerosperma	Stem
	R.alpinus and *R.saxatilis*	Bark
	R.nepalensis	Fruit
	R.californica	Leaf and bark
Emodin (**2**)	*R.formosana*and *R. serrata*	Root
	R.pumila	Stem,bark
	R.prinoides	Fruit, Leaf
	R.cathartica, *R.pubescens*, *R. alaternus* and *R.heterophylla*	Leaf
	R.frangula	Stem bark and branch
	R.sphaerosperma	Stem
	R.procumbens	Whole part
	R.alpinus and *R.saxatilis*	Bark
	R.nakaharai	heartwood
	R.nepalensis	Fruit
	R.californica	Leaf and bark
Physcion (**3**)	*R.formosana*	Root
	R.fallax	Stem, bark
	R.intermedia	Stem
	R.prinoides	Leaf and Stem
	R.frangula	Stem bark and branch

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

Physcion 8-O-β-rutinoside **(21**)	*R.libanoticus*	Bark
	R.pallasri	Bark
Emodinanthrone-6-O-rhamnopyranoside-2',3',4'-triacetate (**22**)	*R.prinoides*	Fruit
Prinoidin (**23**)	*R.prinoides*	Fruit
Prinoidin-emodinbianthrones (**24**)	*R. nepalensis*	Fruit
Rhamnepalins (**25**)	*R. nepalensis*	Fruit
Glucofrangulin (**26**)	*R.prinoides*	Fruit
	R.cathartica	Leaf
1,6,8-trihydroxy-3-methylanthraquinone 1 -O-rhamnosyl (1→2) glucoside (**27**)	*R.formosana*	Root
1,8-dihydroxy-6-methoxy-3- methyl anthraquinones 8-0- rhamnosyl-(1→2)-glucoside (**28**)	*R.formosana*	Root
1,2,6,8 tetrahydroxy-3 methyl anthraquinone 8-O-ß-D-glucopyranoside (**29**)	*R.alaternus*	Root bark and Leaf
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
Flavonoids		
Kaempferol-3-O-β-rhamninoside (**31**)	*R.petiolaris*	Fruit
	R. nakaharai	Heartwood
	R. alaternus	Leaf
Luteolin (**32**)	*R.alaternus*	Leaf
	R.davurica	Bark
Kaempferol (**33**)	*R.alaternus*	Leaf, Fruit
	R.lycioides	Aerial parts
	R.davurica	Bark
	R.saxatilis, R.catharticus and *R.disperma*	Fruit
	R.californica	Leaf and bark
	R.pallasii	Bark

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

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

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

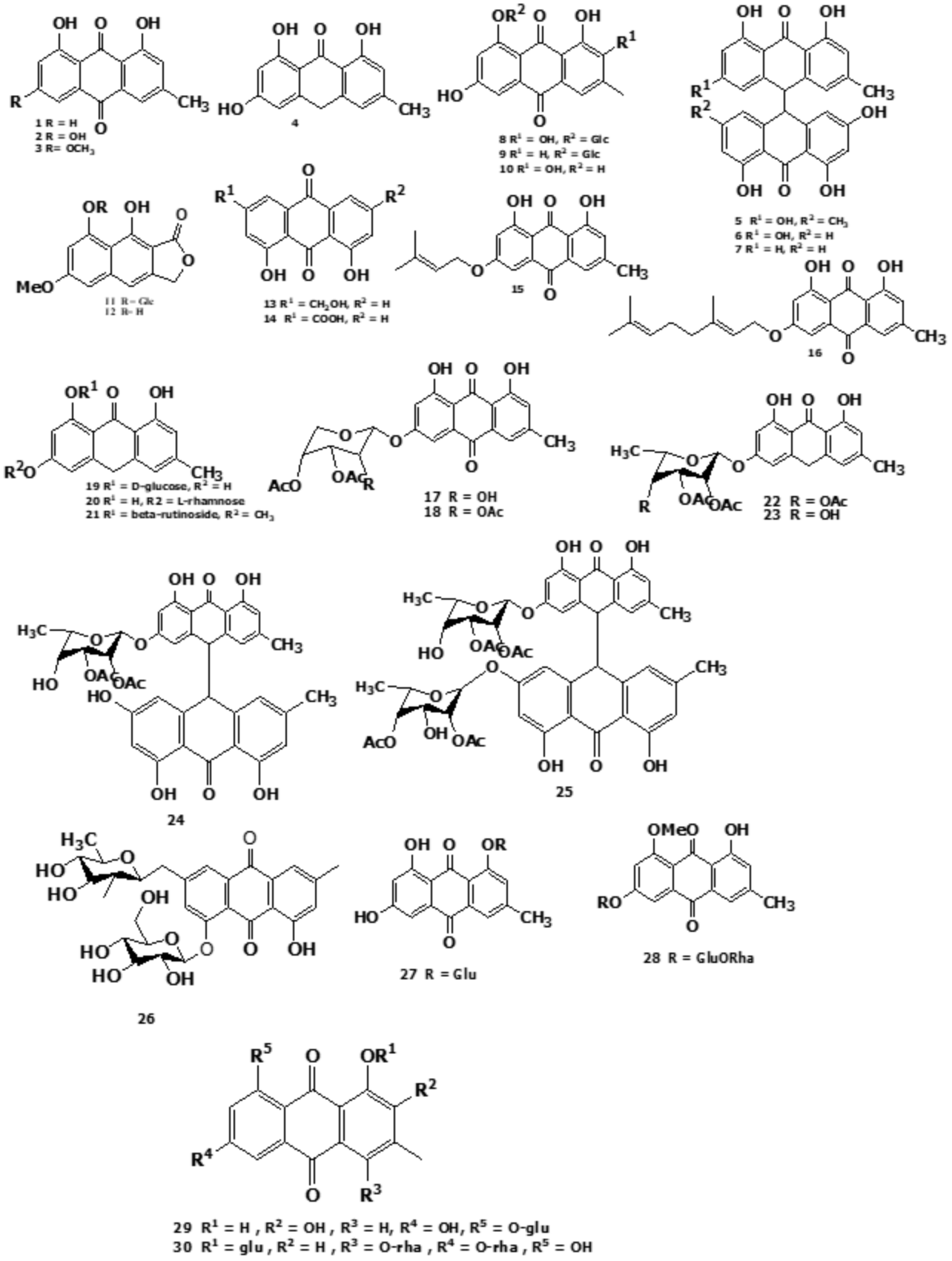

Figure 2: Anthraquinones reported from the genus *Rhamnus.*

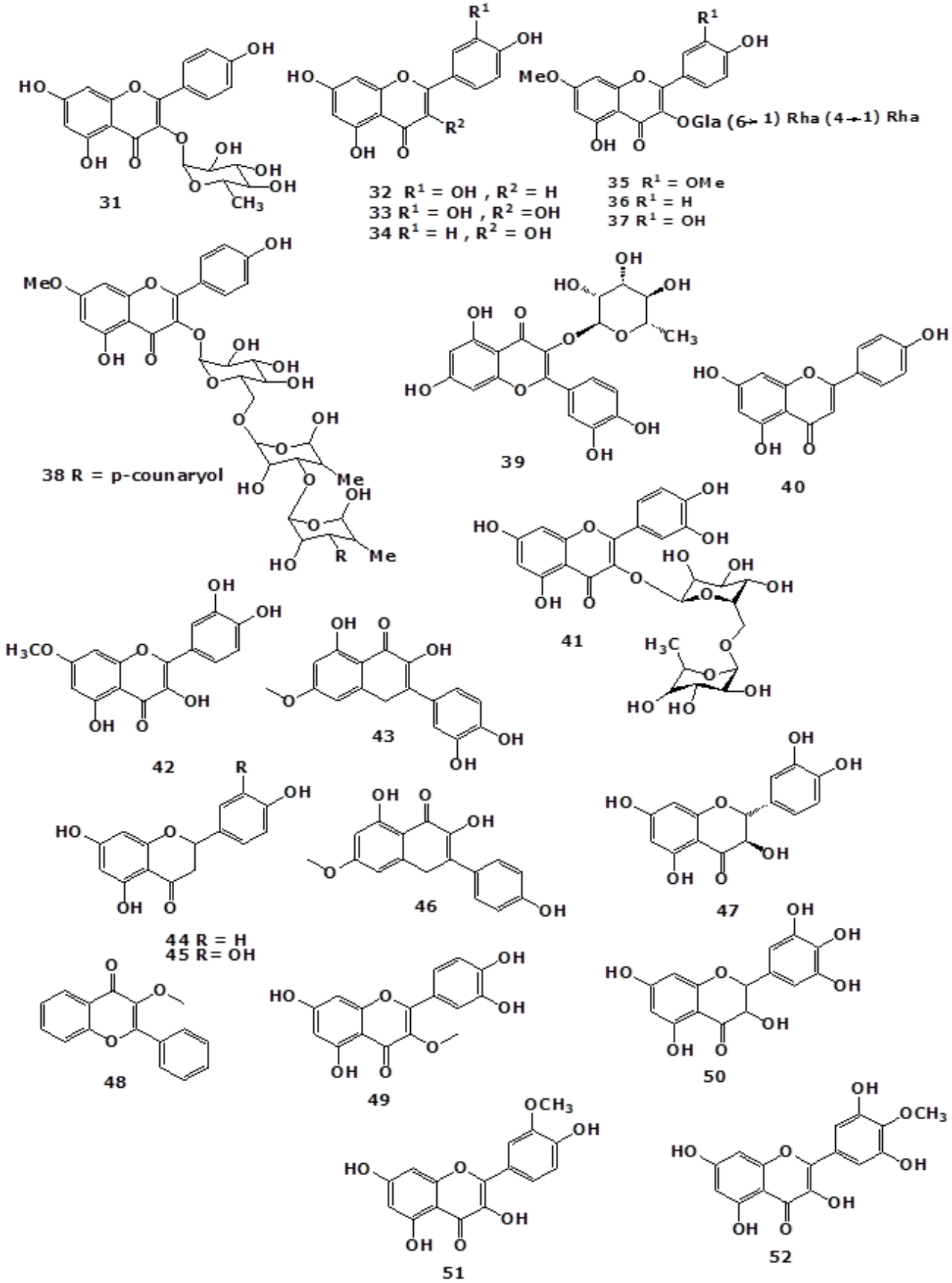

Figure 3: Flavonoids reported from the genus *Rhamnus.*

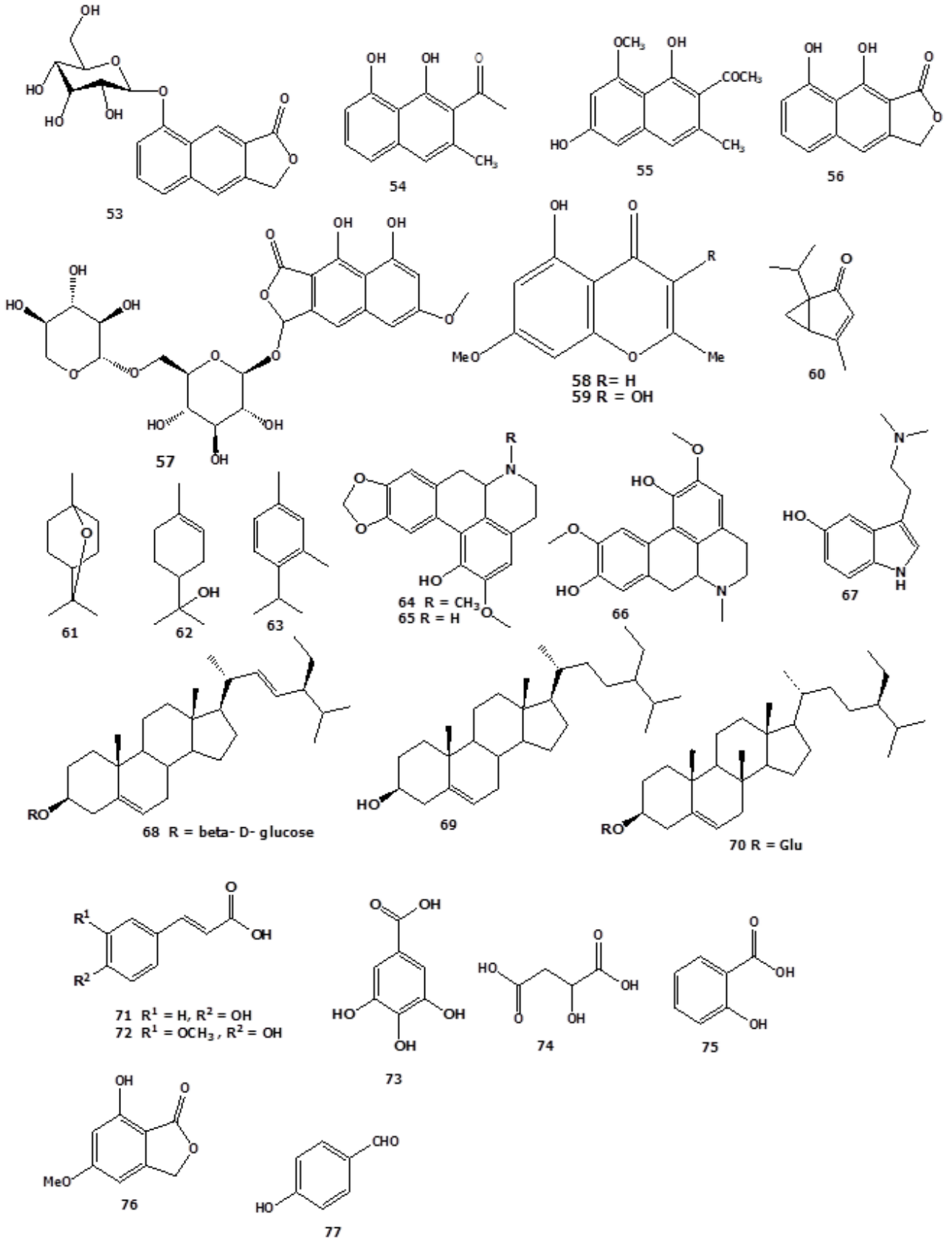

Figure 4 : Napthalenic derivatives, terpenoids, alkaloids, organic acids and other compounds reported from the *genus Rhamnus.*

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
Hepatoprotective	*R. alaternus*	aqueous	leaves	Biochemical and histopathological changes in Wistar rats	Extract reduced levels o Glutamic oxaloacetic tr pyruvic transaminase (G significantly attenuated changes in the liver
Anti-inflammatory	*R. alaternus*	ethanol	Stem bark	Carrageenan-induced rat paw edema assay	extract exhibited anti-infla of 54.50% and 54.77% a as compared the standard showed the inhibition of and 4hr of treatment, resp
Anti-inflammatory	*R. prinoides*	ethanol	Stem and stem bark	Cyclooxygenase (COX-2) assay	extract exhibited activities which was weak activities µg/mL exhibited by ascorb
Anti-inflammatory	*R. davurica*	methanol	bark	Cyclooxygenase (COX-2) assay	The isolated compounds, (**33**) exhibited activities 9.27 µg/mL respectively
Antibacterial	*R. prinoides*	Methanol and chloroform	leaves	Agar well diffusion	Extract exhibited activities *S. pneumoniae,* and *S. ty* and chloroform fractions r mg/mL and from 8.13 respectively.
Antibacterial	*R. californica*	methanol	Leaf and bark	Disc diffusion	Both extracts exhibited a *pyogenes*, *M. smegmatis*, *S. aureus (MRSA*) with MI
Antibacterial	*R. alaterus*	Ethyl acetate and Total Oligomers flavonoids (TOF)	leaves	Microdilution and agar dilution	The TOF extract exhibited *faecalis*, *E. coli*, *S. enter* MIC values of 120 µg/mL µg/mL and 62.5 µg/mL acetate extract exhibited 150µg/mL, 3.75 mg/mL, respectively
Antibacterial	*R. wightii*	Ethyl acetate	Whole part	Agar disc diffusion	Extract exhibited activitie *E. faecalis*, *K.pneumonia*, inhibition zones (in mm) 12 respectively
Antibacterial	*R.*	methanol	Bark	Micro-dilution	All extract exhibited activit

	alaternus,*R. fallax*,*R. intermedia* and *R. pumila*			broth assay	*aeruginosa* and *E. coli* with 1.25 to 2.5 µg/mL
Antibacterial	*R. californica*	methanol	Leaves	Kirby-Bauer disc diffusion	Extract exhibited activities *Methicillin-resistant St cereus*,*Pseudomonas aeru* and *Escherichia coli*with z mm to 14.3 mm
Antibacterial	*R. wightii*	Ethyl acetate	Whole part	Agar disc diffusion	Musizen (**54**) exhibited ac *pneumonia* with MIC valu potent than the standard value of 120 µg/mL
Antifungal	*R. alaternus*, *R. fallax*,*R. intermedia* and *R. pumila*	methanol	Bark	micro-dilution broth assay	All extract exhibited activi and *M.gypseum* with MIC mg/mL against *C. albicans* the plant extracts *R. falla* exhibited with MIC val dermatophyte species (*M.*
Antimalarial	*R. prinoides*	Chloroform	Root bark	ELISA assay	extract exhibited activitie *Plasmodium falciparum* s µg/mL, which was weak a of 0.004 µg/mL exhibite drug
Antimalarial	*R. prinoides*	Hexane& dichloromethane	root	Radioisotope	extracts of hexane and dic activities anti-plasmodia w and 30.3 µg/mL, respectiv
Antimalarial	*R. prinoides and R. staddo*	aqueous	Leaves and root bark	blood-induced CQ-resistant rodent parasite in mice	The plant extract and s potential effects against rodent parasite in mice s in the range 51% -75%
Antioxidant	*R. alaterus*	methanol	Root bark and leaves	DPPH , Xanthine Oxidase (XOD) and Superoxide anion scavenging effects	The root bark and Lea activities with IC_{50} valu respectively, when compa exhibited by α-tocopherol the leaves and root ba oxidase (XOD) inhibiting 103.96 and 83.33 µg scavenging effects with IC as compared with the po

					IC50 value of 37.3 and 6 µ
Antioxidant	*R. petiolaris*	Methanol and aqueous	fruit	DPPH and ABTS assay	Extracts exhibited activ equivalent (TE)/g and 394
Antioxidant	*R. alaternus*	methanol	leaves	DPPH, Xanthine Oxidase and Superoxide anion scavenging effects	Rhamnetin-3-O-β-isorham activities with IC_{50} value antioxidant activity as con exhibited by vitamin E kaempferol 3-O-β-isorhan O-β-isorhamninoside (isorhamninoside (**37**) exh inhibiting with respective µg/mL and superoxide an values of 42, 79 and 3 positive control allopurino 4µg/mL respectively
Antioxidant	*R, alaternus*	methanol	leaf	Super oxide radical scavenging	Kaempferol 3-O-β-isorham 3-O-β-isorhamninoside e values 18.75 and 22.5 µg/
Antioxidant	*R. nakaharai*	methanol	Heart wood	DPPH assay	The isolated compound, a with IC_{50} value of 117 activities compared to IC_5 ascorbic acid the standard
Antioxidant	*R. nakaharai*		Root bark	Iron induced lipid peroxidation	The isolated compound, activities with IC_{50} val comparable to IC_{50} value standard butylated hydrox potent than α- tocopheno values of 3.71 and 97.10 µ
Antioxidant	*R. alaternus*	ethanol	leaves	DPPH assay	extract exhibited activitie which has good antioxida IC_{50} value of 3 butylatedhydroxytoluene (
Antioxidant	*R. alaterus*	Aqueous and ethyl acetate fraction	leaves	Xanthine Oxidase (XOD) and Super oxide anion scavenging	aqueous extract and ethy xanthine oxidase inhibitin 208 and 137µg/mL, and effects with IC_{50} values of
Antioxidant	*R. alaterus*	Methanol-acetone	Leaf and stem bark	DPPH assay and ferric reducing antioxidant potential	leaves and stem bark ex with IC_{50} values of 10.5 which was weak activit 5.6µg/mL exhibited by BH

					activities with EC_{50} va respectively, which was v value of 0.1 µg/mL exhibit
Antioxidant	*R. alaternus*		leaves	Cupric reducing antioxidant (CUPRAC), reducing power assay and ferric reducing antioxidant power (FRAP)	Kaempferol 3-O-β-isorham 3-O-β-isorhamninoside (reduced power assay a mg/mL, while FRAP act concentration 1000 µg/mL by 300 µg/mL and 320 respectively
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 usin with EC_{50} values of 2 respectively, which was g value of 852 µg/mL exhibi control. Similarly, all the p using reducing power as 1.99, 0.81 and 0.99 µ comparable and greater values of 7.53, 1.8 and 7. by BHA, quercetin and asc
Antioxidant	*R. prinoides*	ethanol	Stem and stem bark	DPPH and ABTS assay	The semi purified extract IC_{50} value of 0.2 mg/mL, standard BHT having I Similarly, the crude extra IC_{50} value of 0.0596 mg/ IC_{50} value of BHT, the pos
Antioxidant	*R. triquetra*	methanol	Aerial part	DPPH assay	crude extract and their butanol, chloroform and with IC_{50} values of 70.26, µg/mL respectively, which is more active compared exhibited by the standard
Antioxidant	*R. alaternus*	Methanol and aqueous	leaves	DPPH and β-carotene-linoleic acid assay	The methanol and aque activities with IC_{50} value respectively, which was active compared to IC_{50} v by the standard (BHT). exhibit activities using β-c 89% inhibition, which was by BHT the standard

Antioxidant	*R. alaternus*	methanol	leaves	Oxygen radical absorbance capacity assay (ORAC)	extract exhibited with 6.5 more active as compared mmol TE/g extract
Anti-hyperlipidemia	*R. alaternus*	methanol	leaves	Calculating Malondialdehyde in cultured K562 cells	kaempferol 3-O-β-isorhan O-β-isorhamninoside (isorhamninoside (**37**) f exhibited by calculating (MDA) in cultured K562 leukemia cells with IC_{50} 180,320 and 106 µg/mL, r
Anti-hyperlipidemia	*R. alaternus*	methanol	leaves	Using Hyperlipidemia rats	The Oral crude extract a levels of cholesterol a hepatoma HePG2 and hyperlipidemic rats m respectively, at 200 mg ex
Anti-proliferative	*R. alaternus*	methanol	Root bark and leaf	MTT assay	The root barks and leaf ex K562 cells with IC_{50} valu Similarly the extracts ex cells with IC_{50} value o respectively
Anti-proliferative	*R. davurica*	methanol	bark	sulforhodamine B (SRB)micro culture colorimetric assay	The extract exhibited acti lines HT-29 and SGC-790 89.53 µg/mL. respectively
Anti-proliferative	*R. davurica*	methanol	bark	MTT colorimetric assay	Kaempferol (**33**) exhibi cancer cell lines HT-29, S values of 25.7, 13.43 an the compound apigenin (19.79, 17.76 and 10.20 µg
Wound healing	*R. prinoides*	methanol	leaves	Excision and incision models in adult Swiss albino mice	Treatment with 5 % and ointment exhibited signific both excision and incision
Cytotoxicity	*R. frangula*	hydroalcoholic		MTT assay	Extract exhibited activities (MCF-7) with half maxima value of 10 mg/mL.
Cytotoxicity	*R. alaternus*	Ethyl acetate and Total Oligomers	leaf	MTT assay	TOF extract exhibited ac myelogenous K562 and m values of 75 µg/mL and L1210 cells respectively

		flavonoids			extract showed activities and 176 µg/mL respective
Toxicity	*R. davurica*	ethanol	bark	Sulforhodamine B (SRB) microculture colorimetric assay	Extract exhibited activities cells (L-02) with IC_{50} value
Cytotoxicity	*R. alaternus*	methanol	leaf	Alamar blue assay	kaempferol 3-O-β-isorham 3-O-β-isorhamninoside (**3** human lymphoblastoid TK K3O-ir nor R3O-ir reach proliferation
Cytotoxicity	*R. nepalensis*	methanol	fruit	MTT assay	The isolated compound, p against KB (human epide with IC_{50} value of 0.045 potent than the standard, 0.2 µM
Cytotoxicity	*R. alaternus*	methanol	bark	Trypan blue assay	extract exhibited activiti leukemia cells (U937) wi which was comparable exhibited by taxol the star
Anti-tyrosinase	*R. nakaharai*	methanol	Heart wood	Mushroom tyrosine inhibitory assay	6-methoxysorigenin (**12**) value of 42.2 µM, which w the positive control kojil a
Anti-mutagenicity	*R. alaternus*	aqueous	leaf	Ames assay	The ethyl acetate fractio *Typhimurium* (TA98) stra and 78% inhibition mutag
Antigenotoxic	*R. alaternus*	methanol	leaf	SOS chromo test	kaempferol 3-O-β-isorham 3-O-β-isorhamninoside (**3** concentration (1,5 a antigenotoxicity activities
Antigenotoxic	*R. alaternus*	methanol	leaf	Comet assay	Kaempferol 3-O-β-isorham 3-O-β-isorhamninoside (**3** human lymphoblastoid c concentration, the total D and R3O-ir showed no sign

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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