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Review Article

Natural product diversity of Buckthorns (*Rhamnus cathartica L.* and *Rhamnus disperma Boiss*)

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ABSTRACT

Traditional medicine remains an alternative care option for most poor countries due to its inherent traits, unique and holistic approaches, accessibility, and cost. The current review aims to provide a comprehensive and up-to-date compilation of documented traditional medicinal uses, phytochemicals, and pharmacological activities of invasive R. cathartica and R. disperma, as well as valuable information to support its use as an alternative medicine in future healthcare practice. The genus Rhamnus, commonly called buckthorns, belongs to the family Rhamnaceae. It is considered a fruit and is of nutritional interest owing to its low calories. This review demonstrated that R. cathartica and R. disperma have multifaceted pharmacological potential. Studies examining this compound antioxidant, anticancer, anti-inflammatory, antiviral, and antibacterial characteristics have drawn attention to its effectiveness. Only a small number of research have looked specifically at R. disperma; instead, most studies have looked at R. cathartica, leading to generalized conclusions attributed to the group of compounds rather than the individual component. This paper covers Egyptian Buckthorns' chemistry and pharmacological potential, including their mechanism of action whenever applicable.

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1. *Introduction*

Egypt is one of the planet's most diverse environments and a potential source of numerous phytochemicals with pharmacologically beneficial use [1, 2]. Numerous sources, including plants, animals, marine life, and ancient ecosystems, are rich in phytochemicals [3]. For many years, traditional medical techniques have been used in this field [4, 5]. The plant genus *Rhamnus* has been utilized in traditional medicine to treat a wide range of diseases in many different countries [6]. One of the *Rhamnaceae* family's most significant genera *Rhamnus*, commonly called buckthorn, is a genus of about 110 deciduous or rarely evergreen trees and shrubs that are native to temperate climates. *Rhamnus* species have deciduous or sporadically evergreen foliage and are shrubs or small to medium-sized trees. Branches terminate in a wood spine or remain unarmed. The single, veined leaf blades with pinnate veins. Leaf edges can be whole or serrated, in rare instances. Most species have small, yellowish-green, bisexual, or unisexual, rarely polygamous flowers, or they produce axillary cymes,

cymose racemes, cymose panicles with a few blooms or single flowers. The ovate-triangular, keeled sepals on the adaxial side of the calyx tube are arranged in a campanulate to cup-shaped arrangement [7, 8]. Only two species of buckthorn are found in the Egyptian environment, and they are all found in the Sini and Nile valley regions, according to Egyptian flora [9, 10]. Dried *R. cathartica* bark extract 5% topical gel was prepared and tested against *Cutibacterium acnes*, *Staphylococcus aureus,* and *Staphylococcus epidermidis* [11]. *Rhamnus cathartica* known as the European buckthorn, common buckthorn, purging buckthorn, or just buckthorn, is a species of small tree in the flowering plant family Rhamnaceae.

1. Ethnopharmacology and uses of Buckthorns in folk medicines

In conventional medicine, preparations of *R. cathartica* are also used to treat anus fractures, hemorrhoids, intestinal atonia, chronic constipation, and spastic colitis. An alcoholic tincture is made from the fruits of *R. cathartica* for rubbing during rheumatism (the fruits demand 40% alcohol or vodka). Fresh juice extracted from the fruits of *R. cathartica* may be consumed during treatment; one tablespoon for adults and one teaspoon for children per session. *R. cathartica* does not, however, affect everybody in the same manner; some may get severe diarrhea after ingesting 1 tablespoon of fresh or canned juice. Rinsing the oral cavity externally is done by washing with water. Ripe fruits are used in therapy; green berries are not eaten or used in any other way. The laxative properties of *R. cathartica* promote intestinal motility and tone, but they take time to show results; symptoms appear 10–14 hours after administration. Compared to the crust bark, the fruits have less of an impact. Moreover, fruit infusions and decoctions have diuretic and antibacterial properties. Water extracts from the fruits significantly reduce the growth of the herpes virus. *R. cathartica* is used for gout, gastritis, colitis with diarrhea, clay invasion, and additional ailments not mentioned above in traditional medicine [12].

2. Allelopathy

The plant fruit, leaves, and bark contain secondary chemicals, including emodin, which may shield it from infections, insects, and herbivores [13]. Since emodin **(1)**, is mostly found in unripe fruits, which allow seeds to mature before being spread, it may inhibit early consumption of *R. cathartica* fruit. Birds and mice strongly avoid unripe fruits, and when they do eat them, they either regurgitate the food or pass loose, watery feces [13]. A constitutive emitter of isoprene is *Rhamnus cathartica* [14]. Exudates from *R. cathartica* leaves, fruit, roots, bark, and leaf litter have allelopathic effects that can inhibit the germination of other plant species in the soil. In comparison to typical soils, buckthorn-dominated areas have higher nitrogen and carbon contents [13].

3. Natural product diversity of the Buckthorns

3.1. *Anthraquinone*

Emodin **(1)**, chrysophanol **(2)**, physcion **(3)**, endocrocin **(4)**, sennosid **(5)**, and 20 different types of fatty acids. Detected in the methanol extract of *R. cathartica* bark from Iran, the total ash content percentage is 46.18%, 23.81% of acid-insoluble ash, and 6.52% of water-soluble ash, respectively. 351.66 mg of gallic acid and 23.15 mg of total flavonoids and phenols were found in one gram of dry extract, respectively [15]. Emodin **(1),** 1,8-dihydroxy-2-[(*Z*)-4-methylpenta-1,3-dien-1-yl] anthraquinone **(6)**, 2-acetyl-3,8-dihydroxy-6-methoxyanthraquinone **(7)**, glucofrangulin A **(8),** [(*Z*)-4-methylpenta-1,3-dien-1-yl], 1,8-dihydroxy-2-Dendrochrysanene **(9),** and 1,8-Dihydroxy-2-[(*Z*)-4-methylpenta-1,3-dien-1-yl]anthraquinone **(10)** have been separated from the *R. cathartica* methanol extract that was gathered at Giza, Egypt [16]. Emodin **(1)**, 1,8-dihydroxy-2-[(Z)-4-methylpenta-1,3-dien-1-yl], 2-acetyl-3,8-dihydroxy-6-methoxyanthraquinone **(2)**, 1,8-dihydroxy-2-[(*Z*)-4-methylpenta-1,3-dien-1-yl] anthraquinone **(6)**, glucofrangulin A **(8)** and [(Z)-4-methylpenta-1,3-dien-1-yl], 1,8-dihydroxy-2-[Dendrochrysanene **(9)** 1,8-Dihydroxy-2-[(*Z*)-4-methylpenta-1,3-dien-1-yl]anthraquinone **(10)**, Pruniflorone H **(11)**, and rumejaposide I **(12)** have been separated from the *R. cathartica* methanol extract that was gathered at Giza, Egypt [16].

3.2. Flavonoid

Five flavonols quercetin **(13)**, kaempferol **(14)**, rhamnetin **(15)**, rhamnocitrin **(16)** and rhamnazin **(17)**, isofraxetin **(17)**, quercetin 3-methyl ether **(18)**, eriodictyol **(19)** and taxifolin **(20)**, aglycones (figure 1), were detected in the aqueous ethanol extracts of the fruits and aerial parts *R. disperma* collected from Southern Sinai mountains (Egypt) [17, 18]. Chromatographic investigation of *R. disperma* roots resulted in the isolation of two highly methoxylated flavonoids; quercetin **(13)** and quercetin 3-*O*-methyl ether **(18),** myricetin 3,6,7,3`,4`,5`-*O*-hexamethyl ether **(21)** and myricetin 3,6,7,4`,5`-*O*-pentamethyl ether **(22)** [19].

3.3. Glycoside

Hesperidin **(23)**, and quercetin **(13)**, were found in the methanol extract of *R. cathartica* bark from Iran [15]. Quercetin dirhamnoside (*α*-L-rhamnopyranosyl-(1 → 6)-*O*-*β*-*D*-galactopyranoside) was detected as quercetin 3,4′-di-*O*-*α*-l-rhamnopyranoside **(24)**, kaempferol 3-*O*-robinoside **(25)**, kaempferol 3-*O*-rhamninoside **(26)**, kaempferol 4′-*O*-rhamninoside **(27)**,quercetin 3-*O*-rhamnoside **(28)**, quercetin 3-*O*-galactoside **(29)**, quercetin 7-*O*-galactoside

(30), quercetin 3-*O*-methyl 7-*O*-galactoside **(31)**, quercetin 3-*O*-robinoside **(32)**, quercetin 3-*O*-rhamninoside **(33)**, rhamnetin 3-*O*-rhamninoside **(34)**, rhamnazin 3-*O*-robinoside **(35)**, rhamnazin 3-*O*-rhamninoside **(36)**, rhamnocitrin 3-*O*-rhamninoside **(37)**,and rhamnocitrin 4′-*O*-rhamninoside **(38)** were detected in the aqueous ethanol extracts of the fruits and aerial parts *R. disperma* collected from Southern Sinai mountains (Egypt), (Figure2) [17, 20].

3.4. Miscellaneous phytochemicals

20 different types of fatty acids. Were detected in the methanol extract of *R. cathartica* bark from Iran [15]. β-Sorigenin **(39)** and geshoidin **(40)** were considered lactone isolated from the *R. cathartica* methanol extract and displayed antibacterial activity G-ve [16]. 2,5-dihydroxybenzoic **(41)** and protocatechuic acid **(42)**, phenolic acids were detected in the aqueous ethanol extracts of the fruits and aerial parts of *R. disperma* collected from Southern Sinai mountains (Egypt) [17]. Isofraxetin **(43)** was detected in the aqueous ethanol extracts of the fruits and aerial parts of *R. disperma* collected from the Southern Sinai mountains (Egypt) [17].

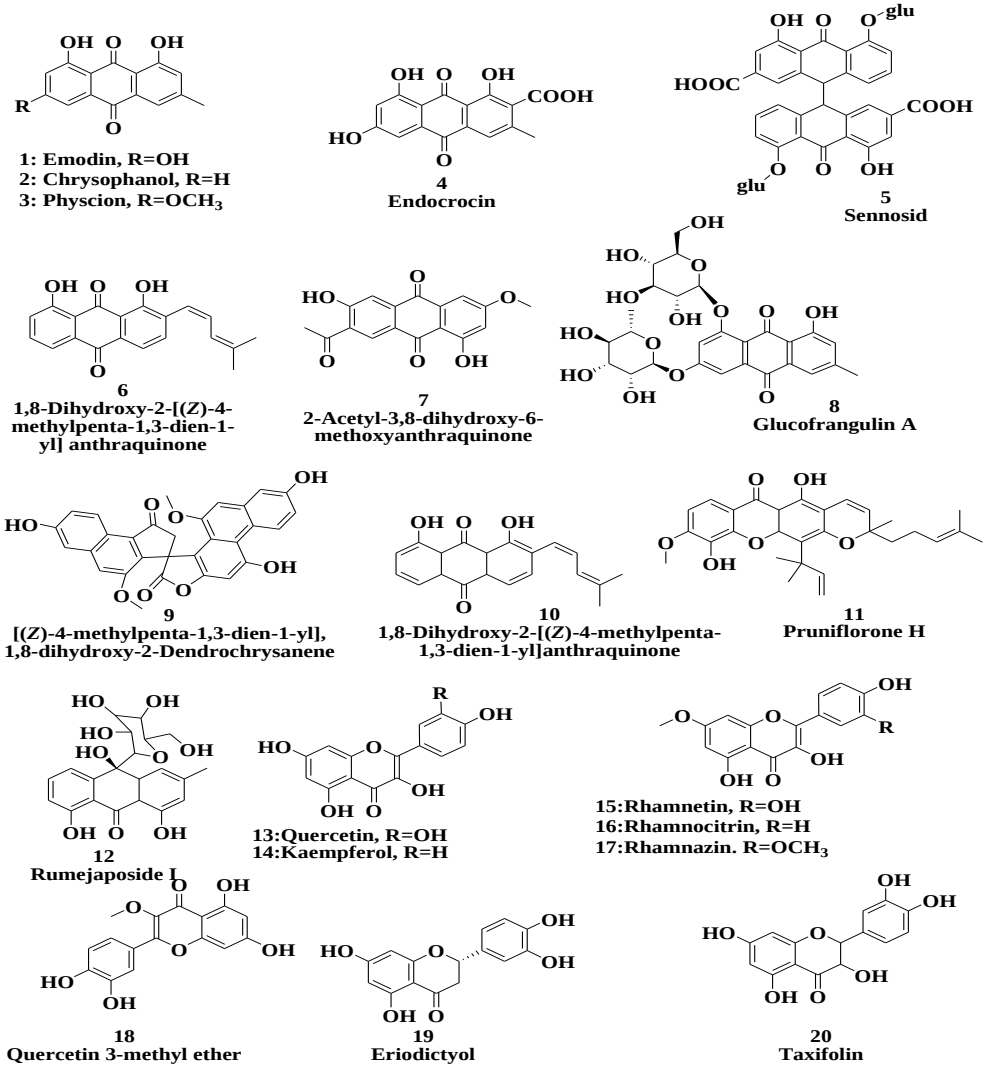
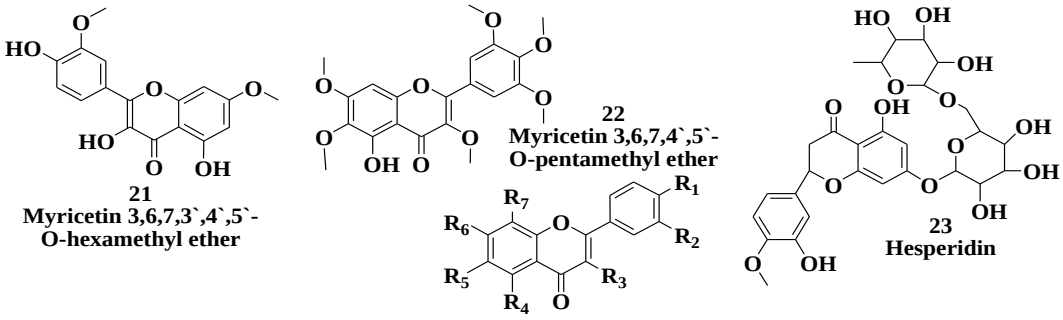


Figure 1: Chemical structure of compounds (1- 20)



	R_1	R_2	R_3	R_4	R_5	R_6	R_7
24: Quercetin 3,4′-di-*O*-α-l-rhamnopyranoside	O-rha	OH	O-rha	OH	H	OH	H
25: Kaempferol 3-*O*-robinoside	OH	H	O-rob	OH	H	OH	H
26: Kaempferol 3-*O*-rhamninoside	OH	H	O-rha	OH	H	OH	H
27: Kaempferol 4′-*O*-rhamninoside	O-rha	OH	OH	H	H	OH	H
28: Quercetin 3-*O*-rhamnoside	OH	OH	O-rha	H	OH	OH	H
29: Quercetin 3-*O*-galactoside	OH	OH	O-gla	H	OH	OH	H
30: Quercetin 7-*O*-galactoside	OH	OH	OH	H	OH	O-gla	H
31: Quercetin 3-*O*-methyl 7-*O*-galactoside	OH	OH	OCH_3	H	OH	O-gla	H
32: Quercetin 3-*O*-robinoside	OH	OH	O-rob	H	OH	OH	H
33: Quercetin 3-*O*-rhamninoside	OH	OH	O-rha	H	OH	OH	H
34: Rhamnetin 3-*O*-rhamninoside	OH	OH	O-rha	H	OH	OCH_3	H
35: Rhamnazin 3-*O*-robinoside	OCH_3	OH	O-rob	H	OH	OCH_3	H
36: Rhamnazin 3-*O*-rhamninoside	OCH_3	OH	O-rha	H	OH	OCH_3	H
37: Rhamnocitrin 3-*O*-rhamninoside	OH	H	O-rha	OH	H	OCH_3	H
38: Rhamnocitrin 4′-*O*-rhamninoside	O-rha	H	OH	OH	H	OCH_3	H

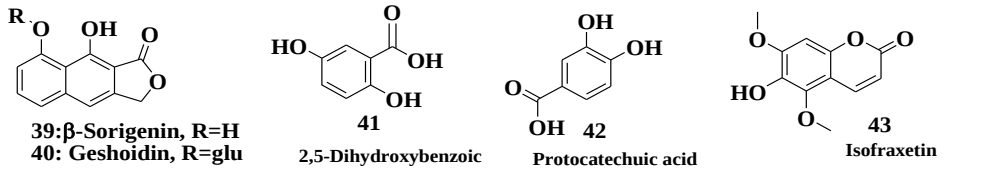


Figure 1: Chemical structure of compounds (21- 43)

4. Pharmacological diversity of the Buckthorns

4.1. Antioxidant properties

Emodin **(1)** (1,3,8-trihydroxy-6-methylanthraquinone) is an essential component of many traditional Chinese medications used to heal ulcers, sore throats, carbuncles, blood stasis, and damp-heat jaundice. Emodin **(1)** has shown additional potential therapeutic uses, including anti-inflammatory, neuroprotective, anti-diabetic, anticancer, and antioxidant properties [21]. The 2,2-Diphenyl-1-picrylhydrazyl (DPPH) test result of methanol extract of *R. cathartica* bark collected from Iran showed an IC_{50} for antioxidant activity of 74.46 g/mL [15]. Rhamnocitrin **(19)** has potent antioxidant properties and is a useful cataract treatment. Thus, using ovine and chick embryo lens models, the anticataract activity of rhamnocitrin (19) (10, 20, 40, and 80 μg) was investigated. In a dose-dependent way, it demonstrated strong protection against cloudiness in lenses caused by hydrocortisone and hydrogen peroxide. Significant anti-catastatic action is seen by rhamnocitrin **(19)**, which is most likely attributed to its antioxidant properties [22]. Pruniflorone H **(15)** showed both

antibacterial activity G-ve and anti-yeast activity, displayed antibacterial activity G-ve [16, 23].

4.2. Anticancer Properties

Emodin **(1)** has a variety of complex molecular processes, some of which include cell cycle arrest, apoptosis induction, and enhanced glutathione S-transferase P, glutathione N-acetyltransferase, and glutathione phase I and phase II detoxification enzyme synthesis [24]. The Caucasian colon adenocarcinoma (HT-29) and human Caucasian gastric adenocarcinoma (AGS) cell lines were found to be affected by the methanol extract of *R. cathartica* bark from Iran. These effects were observed concerning emodin **(1)**, chrysophanol **(2)**, physcion **(3)**, endocrocin **(4)**, sennosid **(5)**, and 20 different types of fatty acids. Compared to the isolated components and the whole extract, they demonstrated a noticeably decreased cytotoxic impact at doses of 100, 200, and 400 g/mL that after 48 hours [15]. Furthermore, Emodin **(1)** has demonstrated efficacy as an anti-cancer drug by efficiently suppressing the proliferation of tumor cell lines in lung, pancreatic, colorectal, hepatocellular carcinoma, and leukemia malignancies [25, 26]. Chrysophanol **(2)** may influence signaling pathways such as Nuclear Factor Kappa B (NF-κB), the mitogen-activated protein kinases (MAPKs), and protein kinase B (PI3K/Akt) signaling pathway, which may have anti-inflammatory, anti-cardiovascular disease (CVD), and anti-cancer properties [27]. Physcion **(3)** has anti-tumor, anti-microbial, anti-inflammatory, antioxidant, optical-related, enzyme-inhibitory, lipid-regulation, and neuroprotective properties. It can also be harmful to the liver, kidneys, and DNA. Following exposure to different doses of physcion **(3)**, the viability of the cervical cancer cells (HeLa) was assessed using the MTT assay. The cell cycle, autophagy marker Light Chain 3 (LC3) expression, apoptosis, alteration in mitochondrial potential, expression of the Bcl-2 protein, and reactive oxygen species levels were investigated using flow cytometry. Physcion **(3)** encumbrance affected HeLa cell viability and the G0/G1 phase of the cell cycle in a concentration-dependent way. Additionally, it was found that the lysosomal system was active, as demonstrated by an increase in autophagic vacuoles, lysosomes, and the characteristic protein LC3. [28]. Miconazole (3 and 10 M) induced abnormal morphological changes and cell death in H9c2 cells. In a dose-dependent manner, rhamnetin **(15)** increased the cellular viability of cells exposed to miconazole (3 M). Rhamnetin **(15)** (1 and 3 M) treatment increased APE/Ref-1 expression while downregulating cleaved caspase 3 in cells driven by miconazole. ROS production was also significantly reduced by rhamnetin **(15)** [29, 30]. Anti-angiogenesis directed against vascular endothelial growth factor receptor 2 (VEGFR2) has emerged as a key element of cancer treatment. There is a long and prosperous history of using natural product discovery as a source of innovative pharmaceuticals. A novel VEGFR2 inhibitor that decreases tumor angiogenesis and proliferation. Human umbilical vascular endothelial cells' (HUVECs) capacity to multiply, move, and form tubes in culture was significantly inhibited by rhamnazin **(17)**. Additionally, it hindered the development of rat aortic ring sprouts. Furthermore, it stopped vascular endothelial growth factor (VEGF) from causing VEGFR2 and its downstream signaling regulator to become phosphorylated in HUVECs. Furthermore, rhamnazin may directly inhibit the growth of MDA-MB-231 breast cancer cells both in vitro and in vivo. Oral therapy with Rhamnazin (20) 200 mg/kg/day might considerably reduce [1, 31]. At the G2–M phase, quercetin 3 methyl ether **(18)** stopped the cell cycle and caused apoptosis. Additionally, it suppressed invasion and migration in human epidermal growth factor receptor 2–negative human breast cancer MCF–7 and T47D cell lines, as well as the triple-negative human breast adenocarcinoma (MDAMB–231) cell line and estrogen receptor-positive/progesterone receptor–positive MCF–7 cell line. Breast cancer cells treated with quercetin 3 methyl ether (39) showed suppression of invasion and migration, apoptosis, and cell cycle arrest. Additionally, it inhibited the development of the mammosphere and the epithelial-mesenchymal transition pathway [32].

4.3. Antimicrobial properties

A 5% topical gel containing dried bark extract of *R. cathartica* was produced and evaluated. Along with figuring out the product's minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) values, its efficacy against *C. acnes*, *S. aureus*, and *S. epidermidis* was evaluated. The product pH ranged from 5.5 to 6. *R. cathartica* 5% gel had minimum inhibitory concentrations (MICs) of 195.3 g/mL, 97.65 g/mL, and 24.41 g/mL against *C. acnes*, S. aureus, and *S. epidermidis*, respectively. Results of the MBC test against *S. aureus*, *S. epidermidis*, and *C. acnes* were 25000 g/mL, 25000 g/mL, and 12500 g/mL, respectively [11]. Emodin **(1)** mainly exhibits mutagenic effects in bacterial systems. It has been shown that emodin **(1)** was a selective inhibitor of the p65lck protein tyrosine kinase and interacts with several cellular targets. Emodin **(1)** can prevent changes in the mammalian cell cycle, which makes it a potentially effective anticancer therapy, especially in cells that overexpress oncogenes [33]. A test for antimicrobial activity was conducted on the *R. cathartica* methanol extract that was gathered at Giza, Egypt, and all identified compounds against *A. niger*, *C. albicans*, *E. coli*, and *S. aureus*.

However, [(*Z*)-4-methylpenta-1,3-dien-1-yl], 1,8-dihydroxy-2-dendrochrysanene **(9)** showed antibacterial activity [G+ve and G-ve]. However, *β*-sorigenin **(39)** showed both antibacterial activity G-ve and anti-yeast activity, whereas 2-acetyl-3,8-dihydroxy-6-methoxyanthraquinone **(7)**, and glucofrangulin A **(8)** displayed antibacterial activity G-ve [16]. Hesperetin had greater antibacterial action against both Gram-positive and Gram-negative bacteria than hesperidin **(23)** [34]. A test for antimicrobial activity was conducted on all identified compounds against *A. niger*, *C. albicans*, *E. coli*, and *S. aureus*. However, dendrochrysanene (12) showed antibacterial activity [G+ve and G-ve]. However, pruniflorone H **(11)** and *β*-sorigenin **(39)** showed both antibacterial activity G-ve and anti-yeast activity, whereas 2-acetyl-3,8-dihydroxy-6-methoxyanthraquinone **(7)**, and glucofrangulin A **(8)** displayed antibacterial activity G-ve [16]. 1,8-dihydroxy-2-[(Z)-4-methylpenta-1,3-dien-1-yl] anthraquinone **(10)** and rhamnocitrin 3-*O*-rhamninoside **(37)** exhibited antibacterial and antifungal activities [16].

4.4. Anti-inflammatory Properties

Emodin **(1)** impressive range of activities extends to combating cardiovascular disease. It targets various molecular pathways that contribute to inflammation, hypertrophy, fibrosis, oxidative damage, and excessive smooth muscle cell proliferation. As a novel form of treatment for cardiovascular disease [35]. In several in vitro and in vivo inflammatory models, emodin **(1)** has demonstrated exceptional anti-inflammatory effects. Treatments for pancreatitis, arthritis, asthma, atherosclerosis, and glomerulonephritis have all shown promise [25]. Rhamnetin **(15)** has a variety of pharmacological properties, including anticancer, anti-inflammatory, antioxidant, antibacterial, and antiviral activities [36]. To investigate rhamnetin **(15)** possible therapeutic relevance, its anti-inflammatory properties and mode of action were investigated in mouse macrophage-derived RAW264.7 cells treated with lipopolysaccharide (LPS) or interferon (IFN). Rhamnetin **(15)** decreased the synthesis of the cytokines mouse tumor necrosis factor (mTNF), mouse macrophage inflammatory protein (mMIP)-1, and mouse MIP-2 in LPS-stimulated macrophages. A harmless dose of rhamnetin **(15)** was found to reduce the production of nitric oxide. It has been found that rhamnetin **(15)** stimulates RAW264.7 cells in response to LPS or IFN. Activities on the p38 mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and cyclooxygenase (COX)-2 pathways influence anti-inflammatory effects [37]. To evaluate the antibacterial, anti-inflammatory, and antioxidant qualities of hesperetin, hesperidin **(23)**, and hesperidin glucoside with different solubility, an in vitro comparison was carried out. Hesperidin **(23)** was converted into hesperetin by enzymatic hydrolysis, whereas hesperidin glucoside which is made up of hesperidin mono-glucoside was produced from hesperidin **(23)** by enzymatic transglycosylation. Hesperidin glucoside, hesperidin **(23)**, and hesperetin were shown to have the lowest levels of cytotoxicity in mouse macrophage RAW264.7 cells. Reduced levels of inflammatory mediators, including prostaglandin E2 (PGE2), nitric oxide (NO), tumor necrosis factor-alpha (TNF-*α*), and interleukin-6 (IL-6), were seen after treatment with each drug. While hesperidin glucoside also showed efficacy at greater doses, hesperetin showed improved efficacy at relatively low quantities [34]. *Rhamenus* often contains the anti-inflammatory flavonoids kaempferol **(14)** and rhamnocitrin **(16)**. Kaempferol **(14)** and rhamnocitrin **(16)** both prevent atherosclerosis. It was demonstrated that kaempferol **(14)** and rhamnocitrin **(16)** were DPPH scavengers with IC_{50} values of 26.10 1.33 and 28.38 3.07 M, respectively. As evidenced by decreased malondialdehyde formation and relative electrophoretic mobility (REM) on agarose gel, kaempferol **(14)** and rhamnocitrin **(16)** both inhibited copper-induced low-density lipoprotein (LDL) oxidation with comparable potency; however, rhamnocitrin **(19)** reduced delayed formation of conjugated dienes better than kaempferol **(14)**. High-cholesterol macrophages are a defining feature of atherogenesis [38]. Rhamnazin (20) is well known for its medicinal activities because of its antibacterial, antitumor, antiangiogenic, and antioxidant properties [39]. To stop acute lung damage from happening, Rhamnazin **(20)** potential as an antioxidant and anti-inflammatory drug was investigated. A study was carried out utilizing a rat animal model to investigate the potential of Rhamnazin **(17)** to mitigate the harm resulting from lipopolysaccharide (LPS). Two days before the intratracheal LPS challenge (5 mg/kg), Rhamnazin **(17)** was administered intraperitoneally (i.p.) at dosages of 5, 10, and 20 mg/kg. The lung wet-dry weight ratio, LDH activity, pulmonary histology, BALF protein content, MPO activity, oxidative stress, and cytokine production were all assessed using a variety of methods. Notably, all inflammatory indicators were significantly reduced and lung histology was visibly improved in the animal groups that were pretreated with Rhamnazin **(17)** [40]. Eriodictyol **(19)** has been expected to explain the mode of action in numerous cellular and molecular pathways due to its significant therapeutic qualities. Studies examining the antioxidant, anti-inflammatory, anti-cancer, neuroprotective, cardioprotective, anti-diabetic, anti-obesity, and other activities of eriodictyol **(19)** have

provided evidence in favor of its therapeutic benefits. Since they may scavenge free radicals, chelate metal ions, and interact with metabolic enzymes. Eriodictyol **(19)**, when applied to RA-FLS for rheumatoid arthritis, changed the expression of pro-inflammatory cytokines, such as TNF-α, and interleukins6 (IL-1, IL-6, and IL-8) [41].

4.5. Nervous System Properties

Hesperidin **(23)** treats and prevents diseases of the central nervous system (CNS). Hesperidin **(23)** inhibits apoptotic and neuro-inflammatory processes to protect the brain [42]. The antioxidant, anti-inflammatory, anti-proliferative, anti-carcinogenic, anti-diabetic, and anti-viral qualities of quercetin **(13)** are among its advantages. Additionally, the lipophilic molecule quercetin **(13)** can cross the Blood-Brain Barrier (BBB) with ease, protecting against neurodegenerative illnesses [43]. *R. cathartica* potential role in an idiopathic neurologic condition in horses resulted from a mouse study to test the plant toxicity. 1,8-Dihydroxy-2-[(Z)-4-methylpenta-1,3-dien-1-yl]anthraquinone **(10)** was used to investigate the antibacterial activity of plants from the genus *R. cathartica* L.[44]. Taxifolin **(20)** is effective in treating Alzheimer's disease. Taxifolin **(20)** alone or with cilostazol, reduces $\alpha\beta$ and C99 levels in N2a Swe cells. It also inhibits amyloidogenesis through downregulation of BACE1 expression by upregulating SIRT1. Taxifolin **(20)** exhibited antiangiogenic properties by inhibiting the development of new blood vessels and branches. Taxifolin **(20)** also inhibited tube formation on the Matrigel matrix in human umbilical vein endothelial cells, indicating its *in vitro* antiangiogenic activity. The effect of taxifolin **(20)** on gastric enzymes and signaling pathways has been proven through various studies. Taxifolin **(20)** can combat postprandial hyperglycemia and inhibit α-amylase in diabetic rats. The results indicate that taxifolin **(20)** effectively inhibits α-amylase and regulates postprandial hyperglycemia, while also providing anti-inflammatory and antioxidant benefits during DM treatment in rats. The assessment of the hyperlipidemic rats treated with taxifolin **(20)** has demonstrated the anti-hyperlipidemic action of taxifolin **(20)**. It preserves the typical lipid profile in the liver, serum, and feces of rats who have been fed a diet high in cholesterol. [45].

4.6. Anti-leishmanial Properties

In vitro tests were done to assess the anti-leishmanial characteristics of *R. cathartica* methanol, hydroalcoholic, and chloroform extracts against the *Leishmania major* parasite. Viability staining and the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) test were used to assess the effects of different dosages on the Leishmania parasite after 12, 24, and 48 hours. The *L. major* parasite was effectively inhibited by *R. cathartica* at all concentrations when it was subjected to extracts of methanol, hydroalcoholic, and chloroform [46].

4.7. Skien care properties

A gel formulation with a raw *R. cathartica* herbal extract in it. The amount of phenolic content in the herbal extract is considerable. Furthermore, the extract exhibited appropriate levels of flavonoids, anthraquinones, and antioxidant properties. The crude extract absorbs UV light quite a little [47]. Four groups (n=5) including normal saline, lipogel base, extract lipogel, and active water were randomly allocated to twenty rats each. A 22 cm full-thickness incision was made in the dorsal region. Evaluations of wound size and histology were conducted on days 3, 5, 7, and 12. The composition including 95% paraffin and 5% polyethylene was selected due to its exceptional skin coverage, uniformity, and consistency. The total amounts of flavonoids and phenolics in *R. cathartica* were 23.415 mg/g and 4.5 mg/g, respectively. Significant differences in wound size were seen between the treatment and control groups based on in vivo data. In studies on histology, *R. cathartica* extract was more effective than other groups in terms of collagen deposition, necrosis, fibroblast maturation, and epidermis development [48]. Chromatographic investigation of *R. disperma* roots resulted in the isolation of two highly methoxylated flavonoids; myricetin 3,6,7,3`,4`,5`-O-hexamethyl ether **(21)** and myricetin 3,6,7,4`,5`-*O*-pentamethyl ether **(22)** together with quercetin **(13)** and quercetin 3-*O*-methyl ether **(18)**. Significant anti-eczematic action was demonstrated by the alcohol extract of *R. disperma* roots, which were taken from Saint Kathrin (Egypt), against mice who were induced to develop eczema. Compared to the group treated with 0.1% w/w of betamethasone ointment, which showed 70% activity in a period of 5–10 days, the alcoholic extract showed a remarkable cure with 80% activity in a time ranging between 3–11 days [19].

4.8. Larvicidal properties

The ability of *R. cathartica* leaf extracts in methanol, chloroform, and petroleum ether to inhibit *Culex pipiens*, a filarial vector, in its third instar larval stage. All of the examined extracts were shown to have larvicidal activity against the third larval instar of *C. pipiens*, however, the petroleum ether extract from *R. cathartica* leaves was more efficient than the methanol and chloroform extracts [49].

4.9. Toxic characteristics

The *R. cathartica* toxic characteristics Following a 34-day feeding study on mice, *R. cathartica* was added in varying doses (0, 5, or 25%) to a full mouse diet following evidence that the plant may be responsible for an idiopathic

neurologic condition in horses. Except for the liver, all major tissues had normal histology and lacked any overt anomalies or clinical signs. The livers of mice given *R. cathartica* showed a pronounced hepatocellular hypertrophy. Sometimes detrimental changes occur in cells that are known as glycogen deposition [44]. Emodin **(1)**, methoxyanthraquinone **(2)**, 1,8-dihydroxy-2-[(*Z*)-4-methylpenta-1,3-dien-1-yl] anthraquinone **(6)**, glucofrangulin A **(8)** [(Z)-4-methylpenta-1,3-dien-1-yl], 1,8-dihydroxy-2-[Dendrochrysanene **(9)** 1,8-dihydroxy-2-[(*Z*)-4-methylpenta-1,3-dien-1-yl], 2-acetyl-3,8-dihydroxy-6-quercetin **(13)**, and kaempferol **(14)**, shown antibacterial activity [G+ve and G-ve] [16]. *R. cathartica* potential role in an idiopathic neurologic condition in horses resulted from a mouse study to test the plant toxicity. 1,8-Dihydroxy-2-[(*Z*)-4-methylpenta-1,3-dien-1-yl]anthraquinone **(10)** was used to investigate the antibacterial activity of plants from the genus *R. cathartica* L.[44].

5. Future Perspectives

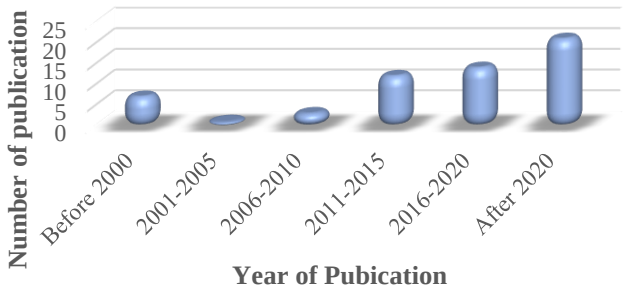


Figure 3. Publication rate of genus buckthorns

This review demonstrated that R. cathartica and R. disperma have multifaceted pharmacological potential. Studies examining this compound antioxidant, anticancer, anti-inflammatory, antiviral, and antibacterial characteristics have drawn attention to its effectiveness. Only a few of research have looked specifically at *R. disperma*; instead, most studies have looked at *R. cathartica*, leading to generalized conclusions that are attributed to the group of compounds rather than the individual component. Further research on the structure-activity connections of the bioactive metabolites derived from buckthorns is necessary to shed light on their potential modes of action as anticancer and anti-inflammatory medicines (Figure 4, Table 1). Discovering the cellular and molecular features of these effects will be of pronounced value in designing new bioactive compounds. Several extracts of Buckthorns are required for further investigation to isolate the compounds responsible for their bioactivities (Table 2). Furthermore, synthetic analogs of bioactive metabolites of the Buckthorns focus on improving the efficacy, and safety, and increasing it is economic production as a food source with further investigation as a natural source of drugs.

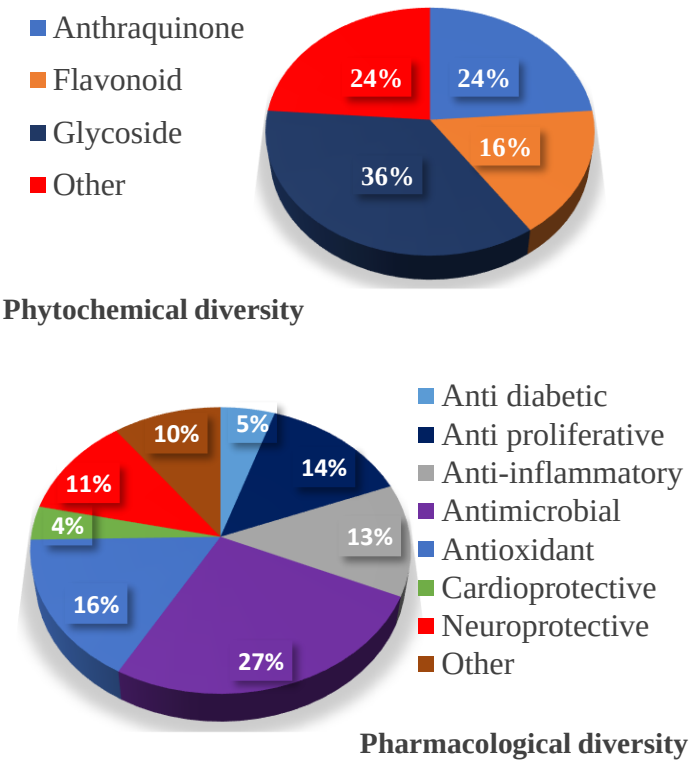


Figure 4: Phytochemical and pharmacological diversity of buckthorns

Table 1. Biological assays related to the therapeutic potential of *buckthorn* compounds.

No.	Compound name	Species	Part used	Extract	Activity	Reference
			Anthraquinone			
1	Emodin	*R. cathartica*	Bark	Methanol	Antioxidant Anti proliferative Antimicrobial Anti-inflammatory Neuroprotective	[21, 35, 46]

					Antidiabetic Cardioprotective	
2	Chrysophanol	*R. cathartica*	Bark	Methanol	Antioxidant Anti proliferative Antimicrobial Anti-inflammatory Neuroprotective Cardioprotective	[46]
3	Physcion	*R. cathartica*	Bark	Methanol	Antioxidant Anti proliferative Antimicrobial Anti-inflammatory Neuroprotective Anti-diabetic Hepatoprotective	[28, 46]
4	Endocrocin	*R. cathartica*	Bark	Methanol	-	[46]
5	Sennosid	*R. cathartica*	Bark	Methanol	-	[46]
6	1,8-Dihydroxy-2-[(*Z*)-4-methylpenta-1,3-dien-1-yl] anthraquinone	*R. cathartica*	Leave	Methanol	Antimicrobial	[16]
7	2-Acetyl-3,8-dihydroxy-6-methoxyanthraquinone	*R. cathartica*	Leave	Methanol	Antimicrobial	[16]
8	Glucofrangulin A	*R. cathartica*	Leave	Methanol	Antimicrobial	[16]
9	[(*Z*)-4-methylpenta-1,3-dien-1-yl], 1,8-dihydroxy-2-Dendrochrysanene	*R. cathartica*	Leave	Methanol	Antimicrobial	[16]
10	1,8-Dihydroxy-2-[(*Z*)-4-methylpenta-1,3-dien-1-yl]anthraquinone	*R. cathartica*	Leave	Methanol	-	[16]
11	Pruniflorone H	*R. cathartica*	Leave	Methanol	Antimicrobial	[16]
12	Rumejaposide I	*R. cathartica*	Leave	Methanol	-	[16]
			Flavonoid			
13	Quercetin	*R. cathartica* *R. disperma*	Bark	Methanol	Antioxidant Anti-proliferative Antimicrobial Anti-inflammatory Neuroprotective	[19, 43, 46]
14	Kaempferol	*R. cathartica* *R. disperma*	Leave	Methanol	-	[44]
15	Rhamnetin	*R. disperma*	Fruit Aerial Parts	Ethanol	Antioxidant Anti-proliferative Antimicrobial Anti-inflammatory	[17, 37]
16	Rhamnocitrin	*R. disperma*	Fruit Aerial Parts	Ethanol	Anti-inflammatory	[17, 50]
17	Rhamnazin	*R. disperma*	Fruit Aerial Parts	Ethanol	Antioxidant Anti-proliferative Antimicrobial Anti-inflammatory Cardioprotective	[17, 39]
18	Quercetin 3-methyl ether	*R. disperma*	Fruit Aerial Parts	Ethanol	Antioxidant Anti proliferative Antimicrobial	[17, 32] [19]
19	Eriodictyol	*R. disperma*	Fruit Aerial Parts	Ethanol	Antioxidant Anti proliferative Antimicrobial	[17, 41]

					Anti-inflammatory Neuroprotective Anti-diabetic Anti-obesity	
20	Taxifolin	*R. disperma*	Fruit Aerial Parts	Ethanol	Antioxidant Anti-proliferative Antimicrobial Anti-inflammatory Antiangiogenic	[45]
21	Myricetin 3,6,7,3`,4`,5`-*O*-hexamethyl ether	*R. disperma*	Root	Ethanol	-	[19]
22	Myricetin 3,6,7,4`,5`-*O*-pentamethyl ether	*R. disperma*	Root	Ethanol	-	[19]
	Glycosides					
23	Hesperidin	*R. cathartica*	Bark	Methanol	Antioxidant Anti-proliferative Antimicrobial Anti-inflammatory Neuroprotective	[42, 46]
24	Quercetin 3,4′-di-*O*-α-l-rhamnopyranoside	*R. disperma*	Fruit Aerial Parts	Ethanol	-	[17]
25	Kaempferol 3-*O*-robinoside	*R. disperma*	Fruit Aerial Parts	Ethanol	-	[17]
26	Kaempferol 3-*O*-rhamninoside	*R. disperma*	Fruit Aerial Parts	Ethanol	-	[17]
27	Kaempferol 4′-*O*-rhamninoside	*R. disperma*	Fruit Aerial Parts	Ethanol	-	[17]
28	Quercetin 3-*O*-rhamnoside	*R. disperma*	Fruit Aerial Parts	Ethanol	-	[17]
29	Quercetin 3-*O*-galactoside	*R. disperma*	Fruit Aerial Parts	Ethanol	-	[17]
30	Quercetin 7-*O*-galactoside	*R. disperma*	Fruit Aerial Parts	Ethanol	-	[17]
31	Quercetin 3-*O*-methyl 7-O-galactoside	*R. disperma*	Fruit Aerial Parts	Ethanol	-	[17]
32	Quercetin 3-*O*-robinoside	*R. disperma*	Fruit Aerial Parts	Ethanol	-	[17]
33	Quercetin 3-*O*-rhamninoside	*R. disperma*	Fruit Aerial Parts	Ethanol	-	[17]
34	Rhamnetin 3-*O*-rhamninoside	*R. disperma*	Fruit Aerial Parts	Ethanol	-	[17]
35	Rhamnazin 3-*O*-robinoside	*R. disperma*	Fruit Aerial Parts	Ethanol	-	[17]
36	Rhamnazin 3-*O*-rhamninoside	*R. disperma*	Fruit Aerial Parts	Ethanol	-	[17]
37	Rhamnocitrin 3-*O*-rhamninoside	*R. disperma*	Fruit Aerial Parts	Ethanol	Antimicrobial	[16, 17]
38	Rhamnocitrin 4′-*O*-rhamninoside	*R. disperma*	Fruit Aerial Parts	Ethanol	-	[17]
	Miscellaneous phytochemicals					
39	β-Sorigenin	*R. cathartica*	Leave	Methanol	Antimicrobial	[16]
40	Geshoidin	*R. cathartica*	Leave	Methanol	Antimicrobial	[16]
41	2,5-Dihydroxybenzoic	*R. disperma*	Fruit Aerial Parts	Ethanol	-	[17]
42	Protocatechuic acid	*R. disperma*	Fruit Aerial Parts	Ethanol	Antioxidant Anti-proliferative	[17, 51]

					Antimicrobial Anti-inflammatory Neuroprotective Anti-diabetic Hepatoprotective Analgesic Antiatherogenic	
43	Isofraxetin	*R. disperma*	Fruit Aerial Parts	Ethanol	-	[17]

Table 2. Biological assays related to the therapeutic potential of *buckthorn* Extracts.

No.	Species	Extract	Part used	Activity	Reference
1	*R. cathartica*	methanol	bark	Antioxidant Anti-proliferative Antimicrobial	[15]
2	*R. cathartica*	Methanol Hydroalcoholic chloroform	Plant	Anti-leishmanial	[46]
3	*R. cathartica*	Methanol	bark	Antimicrobial	[11]
4	*R. cathartica*	Methanol	bark	Antioxidant Sunscreen	[47]
5	*R. cathartica*	Methanol Chloroform petroleum ether	Leaves	larvicidal	[49]
6	*R. cathartica*	Methanol	Leaves	Antimicrobial	[52]
7	*R. disperma*	Aqueous ethanol	Fruit aerial part	neuroprotective	[17]
8	*R. disperma*	alcoholic	root	Anti eczema	[19]

6. Conclusions

Traditional medicine remains an alternative medical option for many impoverished nations due to its intrinsic characteristics, distinct and comprehensive methods, accessibility, and affordability. The purpose of this review is to provide a comprehensive and up-to-date compilation of documented traditional medicinal uses, phytochemicals, and pharmacological activities of invasive *R. cathartica* and *R. disperma*, as well as valuable information to support their use as an alternative medicine in future healthcare practice. The most frequent components discovered in *R. cathartica* and *R. disperma* are phytochemicals such as anthraquinones and flavonoids, with polyphenols being particularly abundant and possessing potent antioxidant, wound healing, and anti-inflammatory activities. Emodin **(1)** and rhamnocitrin 3-*O*-rhamninoside **(34)** are examples of pharmacological leads from *R. cathartica* and *R. disperma* with anti-proliferative, antibacterial, anti-inflammatory, neuroprotective, and anti-diabetic properties.

Ethical approval

In this study, animal experiments were not applicable.

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Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Author Contribution Statement

M.I.R., W.M.F., A.D., and N.H.Y. collected a complete survey of all compounds and their biological activities isolated from Egyptian Buckthorns. M.I.R. wrote the manuscript. W.M.F. and N.H.Y. revised the surveyed literature data. N.H.Y. and M.I.R. discussed the results scientifically and contributed to the design and editing of the review. All authors reviewed the final manuscript.

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