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Review Article

Phytochemicals, Traditional Uses and Pharmacological Activity of *Rhamnus prinoides*: A Review

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Abstract: *Rhamnus prinoides* L'Herit belongs to Rhamnaceae family widely distributed in India, Eastern, Central and Southern Africa. In Ethiopia it is commonly known as Gesho (Amharic, Tigrigna and Afan Oromo), Gishe (Guragegna) and Geshu (Agewgna). Decoction of the leaves is recommended as remedy for treatment of variety of diseases such as back pain, malaria, pneumonia, sexually transmitted disease, skin infections, wounds, blood purifiers, water borne diseases and as ethnoveterinary medicine. Various secondary metabolites such as flavonoids, alkaloids, tannins, terpenoids, saponins, steroids and anthraquinones have been reported from the genus of which polyphenols were abundant with tremedousantioxidant, wound healing and antiinflammatory activities. The plant also serve as hopping agent, making traditional alcoholic beverages like tella and tej (in Ethiopia), animal feed, medicine, nectar for bees, soil conservation, ornamental, shade and dyes in textiles. This review presents chemical profile as well as biological activities of the species which confirmed that the plant is a good source natural polyphenols and provided valuable information in support of its use as an alternative medicine for future healthcare practice.

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1. INTRODUCTION

Traditional and complementary medicine is an essential and often underestimated health resourcewith many applications, especially in prevention and management of lifestyle-related chronic diseases. Many countries are expanding coverage ofessential health services at a time when consumer expectations for care are rising, costs are soaring andmost budgets are either stagnant or being reduced contributing to the revival of alternative traditional medicine. In developing contries, traditional medicine is the main source of healthcare and sometimes the only source of care, due to its closeness to the ordinary rural communities and its accessibility and affordability in view of the rising healthcare costs (Abebe *et al*., 2003).

Rhamnus prinoides (Figure 1), known as Gesho (Amharic, Tigrigna and Afan Oromo), Gishe (Guragegna) and Geshu (Agewgna) in Ethiopia, belongs to *Rhamanceae* family (Tesema *et al*., 1993) widely distributed in India, East, Central and South African countries (Dlamini and Turner, 2002). The only two *Rhamnus* species that occur in Africa are *R. prinoides* and *R.*

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Staddo (Abegaz *et al*., 1999). The genus name '*Rhamnus*'is derived from an ancient Greek word *rhamnos* for blackthorn meaning a 'tuft of branches' and the species name *prinoides* means 'resembling prion' which is an ever green oak. The genus *Rhamnus* comprises about 150 species of shrubs and small trees occurs both intemperate and tropical countries (Chen and Schirarend, 2007). *R. prinoides* also known as *R. pauciflorus* Hochst. ex A. Rich or *R. celifollius* Kallogg is a climbing shrub or small tree that grows up to 4 m high (Schmidt *et al*., 2002). In Ethiopia, *R.prinoides* (Gesho) is used to add flavour to the local drinks, tella and tej brewed from fermented barley, sorghum or finger millet(d'Avigdor *et al*., 2014; Tesema *et al*., 1993). In Angloa, the bark is used to induce vomiting (Dlamini and Turner, 2002).In South Africa, a decoction of the root is taken to cleanse the blood by the Zulu and to treat pneumonia by the Sotho(Coates-Palgrave, 1988).The boiled soup of the root is used for the treatment of common cold, leaves are used for chest pain and leaves as well as stems are used for the treatment of tonsil in central Kenya(Njoroge & Bussmann, 2006).In a related study in Kenya, it was reported that the leaves are used in preparation of the "muteta″soup used as an appetizer (Mwangi, 2005).

The decoction of the leaves is recommended as remedy for treatment of variety of diseases such as back pain, malaria, pneumonia, sexually transmitted disease, skin infections, wounds, blood purifiers, water borne diseases and as ethnoveterinary medicine (Berhanu, 2014; Enyew *et al*., 2014; Fratkin, 1996; Megersa *et al*., 2013; Muthee *et al*., 2011; Njoroge & Bussmann, 2006; Prozesky *et al*., 2001; Sobiecki, 2002).The leaves are maily used in traditional medicine followed by roots (Araya *et al*., 2015; Diallo *et al*., 2002; Giday *et al*., 2010; Seid & Aydagnehum, 2013). Various class of secondary metabolites such as flavonoids, alkaloids, tannins, terpenoids, saponins, steroids and anthraquinones have been reported from the genus of which polyphenols were abundant withtremendous antioxidant and antiinflammatory activities (Chen *et al*., 2020). The plant also serve as an important hopping agent, making traditional alcoholic beverages like tella and tej (in Ethiopia), animal feed, medicine, nectar for bees, soil conservation, ornamental, shade and dyes in textiles. This review presents a comprehensive overview of the chemical profile as well as biological activities of the plant underlining remarkable activities demonstrated by various parts of the plant supporting its potential use asan alternative medicine for future healthcare practice.

Figure 1. Photo of *Rhamnus prinoides* (Amabye, 2015; Molla, 2015, respectively).

1.1. Botanical Distribution

The plant grows up to 8 m in height and has globular, glossy and serrated leaves. The leaves size varies from 10-125 mm (Vetter, 1997). It is commonly cultivated between altitudes of 1400 to 3200 m above sea level (Nielsen, 1992). The flowers are light yellow-green, solitary up to 20 mm (Orwa *et al*., 2009). The plant is commonly distributed in African countries such as Tanzania, Uganda, exotic to Kenya, Ethiopia, Eretria, Angola, Malawi, Mozambique, Zambia,

Zimbabwe, Cameron, Democratic Republic of Congo and South Africa (Abegaz, 1996; Dlamini & Turner, 2002; Edwards, 1991; Orwa *et al*., 2009).

1.2. Ethnomedicinal uses

The leaves, fruits, roots, seeds, shoots and barks are reported to possess diverse traditional medicinal uses to heal various human as well as animal diseases (Table 1). In Tanzania, a root decoction of *R. prinoides* is mixed with bark of *Erythrina abyssinica* Lam. ex DC as remedy for colics (Chhabra *et al*., 1984).In Ethiopia, the leaf often mixed with the root of *Rubus apetalus* Poir., is boiled, decocted and drunk before meal as remedy for sexually transmitted diseases (Tuasha et al., 2018). The leaf decoction is used for treatment of animal diarrhea and intestinal parasites (Bekele & Musa, 2009), hepatitis (Yineger *et al*., 2007) and leech infestation (Bekele *et al*., 2012).

1.3. Economic Uses

R. prinoides has remarkable importance for nutrition, medicine, or other religious purposesin Africa. The leaves and stems are used to add flavor for the preparation of traditional alcoholic beverages like tella and tej (in Ethiopia) by mixing with other components responsible for the bitter taste. It maintains acidic pH during tella fermentation, so it is used to modify the nature of mesh growth of micro-flora and inhibits the growth of undesirable microorganisms (Kebede, 1994; Van Vuuren *et al*., 1979). It is estimated that close to 5 million people consume it every day (Abegaz & Kebede, 1995; Ashenafi, 2006; Hayeshi *et al*., 2004). The leaves and stems also serve as a commercial hopping agent in the brewery industry that can be used as an alternative substitute hop(Berhanu, 2014). In a related study, the leaves are also proved to serve as potential dye with direct affinity to cotton fabrics (Kechi *et al*., 2013; Tewachew *et al*., 2018). Farmers also use the plant to protect soil erosion and retaining soil on sloping land (Fernandes *et al*., 1984).

1.4. Nutritional Content Analysis

Nutritional content analysis of *R. prinoides* showed that it has protein (8.5%), fiber (25.6%), ash (9.5%), carbohydrate (70.5%), moisture (9.5%) and fat (3.5%) in support of its nutritional significance (Amabye, 2015)

Table 1. Ethnomedicinal uses of *R. prinoides*in Africa.

Disease treated	Plant part	Mode of preparation and administration	Country practiced	Reference
Sexually transmitted diseases, arthritis, flu/cold, back pains, stomachache, pneumonia, brucellosis, strength/nutrient supplement, enhancing/facilitating digestion	Tree	-	Kenya	(Kiringe, 2006)
Ear, nose and throat (ENT) diseases (chest pain, common cold and Tonsil)	Roots, Leaves, Stems	Roots, Leaves and Roots/ stems boiling taking orally respectively	Kenya	(Njoroge & Bussmann, 2006)
Tinea capitis, Itching/skin rash	Seeds, Leaves	Rubbed seeds on the affected part and Burn leaves in oven, crush, mix it with butter and apply on the skin	Ethiopia	(Hishe & Asfaw, 2014; Teklay *et al*., 2013)
Tonsilities	Leaves	Leaves infusion Gargle to rinse the throat	Ethiopia	(Kidane *et al*., 2014; Teka *et al*., 2020)
Skin infection	Leaves	Fresh leaves rubbed it the affected part	Ethiopia	(Tamene, 2020)
Wound	Leaves	Crush the leaf and apply to the wound till the wound cures.	Ethiopia	(Bitew *et al*., 2019)
Tonsillitis	Leaves	Mothers chewing the leaves and spit to mouth of their children whereas young ones chew it for themselves	Ethiopia	(Araya *et al.*, 2015; Tegene, 2018; Teklehaymanot & Giday, 2007)
Eczema	Leaves	Leaves crushed, mixed with pure butter and dressing the affected part		
Scabies	Leaves	The leaf is crushed, powdered, mixed with butter and creamed Wounds and exposing the sunlight for few minutes.	Ethiopia	(Gebeyehu, 2016)
Tonsillitis	Fruits & Shoots	Three fruits and shoots are crushed with three fruits of malt barley, squeezed and droplets of juice are taken through the nose.		
Ring worm	Seed	Adding the grinded powder	Ethiopia	(Abdeta e*t al*., 2020)

Table 1. *Continued.*

Fever in children	Leaves	Adding the leaf in to water, stay for a while and give the drop of this Concoction to the child	Ethiopia	(Asmare *et al*., 2018)
Sedative, gonorrhea, blood purifier, colics	Leaves, roots	Decoction of leaves is sedative; decoction of roots drunk against gonorrhoea and rheumatism; its decoction mixed with that of the bark of *Erythrinaabyssinica*Lam. ex DCalleviates colics; decoction of the roots is considered blood purifier and plant liniment is used for sprains	Tanzania	(Chhabra *et al*., 1984)
Malaria	Bark, roots	-	South Africa	(Cock *et al*., 2019)
Blood cleaning, pneumonia, rheumatism, sprains, gargle, skin complaints, respiratory infections, sexually transmitted disease, arthritis, stomach ache, headache	Fruit, leaves, stems, seeds, roots	-	South Africa	(Dzoyem *et al*., 2016)
Sexual Transmitted Infection	Root	A 3 finger thick pieces of root palm length are boiled in 2 liters of water. 200mls is taken 3 times daily for 7 days	Kenya	(Gakuya *et al*., 2015)
Malaria, backaches	Root bark	Root bark boiled all day and drunk with goat fat for malaria, backaches. Drink only one cup, one time	Kenya	(Koch *et al*., 2005)

Table 1. *Continued.*

Sexually transmitted diseases (STDs)	Leaves	The leaf, often with the root of *Rubusapetalus*Poir., is boiled, decocted, and drunk before meal	Ethiopia	(Tuasha *et al*., 2018)
Tuberculosis	Leaves	-	Uganda	(Tabuti *et al*., 2010)
Dandruff	Leaves	-	Ethiopia	(Mesfin *et al*., 2013)
Waterborne and related diseases	Leaves		Ethiopia	(Siyum & Woyessa, 2013)
Animal diarrhea and intestinal parasites	Leaves	Chopped leaves mixed little water and then filtered then taken orally	Ethiopia	(Bekele & Musa, 2009)
Animal hepatitis	Leaves	Crushed and powdered leaves of *Cheilanthes farinosa*Forsk. Kaulf.and *Rhamnus prinoides*; and whole parts of *Crepis rueppellii* are brushed over the body	Ethiopia	(Yineger *et al*., 2007)
Leech infestation	Leaves	Pounded leaves applied nasally	Ethiopia	(Bekele *et al*., 2012)
Psychoactive agent	Bark	Ground bark that is administered as snuff for mental disorders	South Africa	(Sobiecki, 2002)

1.5. Mineral Content

Mineral contentanalysis of leaves and stem revealed the presence of Ca, Mg, Cr, Mn, Fe, Co, Ni, Cu, Zn, Cd and Pb of which the concentration of Ca and Mg was reported to be high (Gebre and Chandravanshi, 2012, Table 2). In a related study potassium, sodium and magnesium were the most abundant elements from the leaves and stems samples collected from the low-altitude (1500-1670 m above sea level) and medium-altitude (1670-2000 m above sea level) areas (Nagari & Abebaw, 2013).

Table 2. The mineral content of *R. prinoides.*

Constituents (mg/Kg)	Leaf (mg/kg)	Stem (mg/kg)
Ca	6304-22236	3601- 5675
Mg	3202-5706	2635 - 5568
Cr	5.08 - 20.6	ND - 16.3
Mn	8.12 - 17.9	2.16 - 3.98
Fe	47.9 - 187	22 - 124
Co	22.2 -42.1	18.7 - 91.7
Ni	12.8 - 27.3	9.68 - 19.2
Cu	6.5 - 73.0	16.8 - 233
Zn	12.2 - 43	17.4 - 28.2
Cd	0.81 - 3.10	ND - 1.56
Pb	11.7 - 25	ND

ND – Not detected

1.6. Chemical Constituents

Various class of secondary metabolites including alkaloids, triterepenes, saponins, tannins, phenols, cardiac glycosides, anthraquinones, polyphenols and flavonoids were reported from different parts of *R.prinoides* (Amabye, 2015; Co *et al*., 1990; Lin *et al.*, 1991; Lin *et al*., 1990; Molla *et al.*, 2016; Ozipek *et al*., 1994) as summerized here below (Figure 2, Table 3).

Campbell and his co-workers (2019) reported the presence of numerous essential oils from the leaves of *R. prinoides* of which 4-hydroxy-4-methyl-2-pentanone (15, Figure 3) and ethyl 4-ethoxybenzoate (16, Figure 3) account for more than 85% and exhibited significant antibiofilm activity. In a related study, it has been reported that the essential oils have antibacterial, antifungal, antioxidant and anti-diabetic activties (Sut *et al*., 2020).

Figure 2. Structures of compounds isolated from *R. prinoides*.

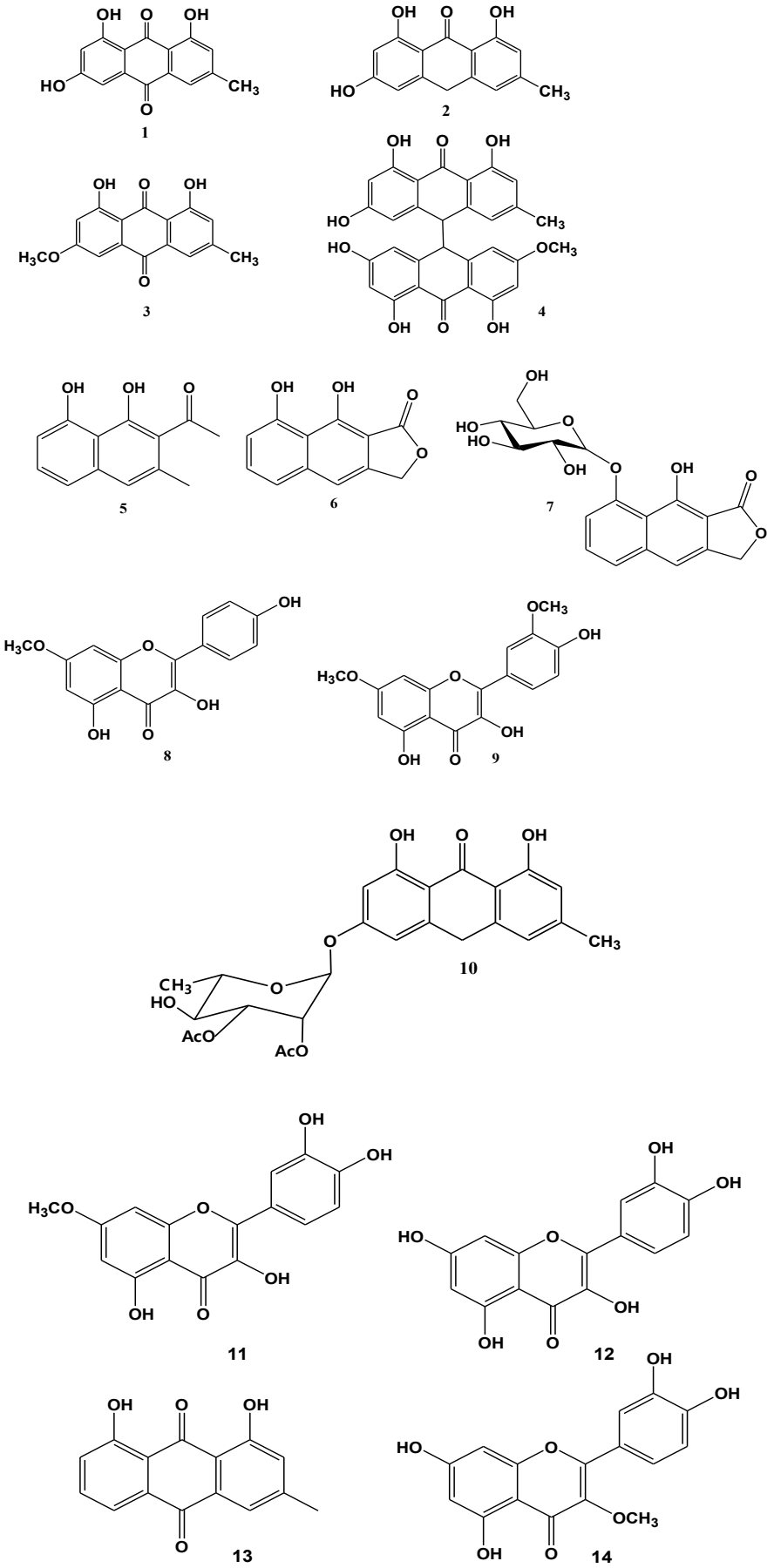
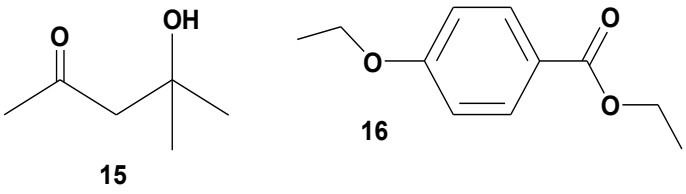


Table 3. Secondary metabolites isolated from *R. prinoides*.

Compound	Plant Part	Reference
Emodin (1)	Fruit, Leaves, stems	(Abegaz & Dagne, 1988; Abegaz & Kebede, 1995; Gebru, 2010)
Emodinanthrone (2)	Leaves, stems, Fruit	(Abegaz & Dagne, 1988; Abegaz & Peter, 1995)
Physcion (3)	Fruit, Leaves, stems	(Abegaz & Dagne, 1988; Abegaz & Kebede, 1995; Gebru, 2010)
Emodinbianthrone (4)	Fruit	(Abegaz & Dagne, 1988; Abegaz & Peter, 1995)
Musizin (5)	Leaves	(Abegaz & Kebede, 1995)
β-sorigenin (6)	Leaves, roots	(Abegaz & Kebede, 1995; Gebru, 2010)
Geshoidin (P-Sorigenin-8-*O*-β-D-glucoside (7)	Leaves, stems, roots	(Abegaz & Kebede, 1995; Gebru, 2010)
Rhamnocitrin (8)	Leaves	(Abegaz & Kebede, 1995)
Rhamnazin (9)	Leaves, roots	(Abegaz & Kebede, 1995; Gebru, 2010)
Prinoidin (10)	Fruits	(Abegaz & Kebede, 1995; Abegaz & Peter, 1995)
Rhamnetin (11)	Leaves, stems	(Abegaz & Kebede, 1995)
Quercetin (12)	Leaves	(Abegaz & Kebede, 1995)
Chrysophanol (13)	Leaves, stems, roots	(Abegaz & Kebede, 1995; Gebru, 2010)
3-*O*-Methylquercetin (14)	Leaves, Stems	(Abegaz & Kebede, 1995)

Figure 3. Structure of major constituents of essential oils from leaves of *R. prinoides*.



1.7. Biological Activity

1.7.1. *Antioxidant activity*

It was reported that *n*-hexane, chloroform, ethyl acetate, and methanolic extracts of the leaf and stem bark of *R.prinoids* possess antioxidant activities by DPPH assay with IC_{50} values of >3000, >3000, >3000, 950.42, ~1500, 710.50, ~1000 and 902.78 µg mL^{-1}, respectively (Pillai *et al*., 2019). The documented antioxidant activities of *R.prinoides*are probably due to flavonoids and polyphenols reported from leaves, stems and roots(Amabye, 2015; Molla *et al*., 2016; Pillai *et al*., 2019).

1.7.2. *Antiinflammatory activity*

Semi purified ethanolic stem and stem bark extracts of *R.prinoides* with higher contents of polyphenols and flavonoids displayed anti-inflammatory activity through reducing the Nitric

Oxide production at the dosage of 11.11-100 µg/mL and the COX-2 inhibitory activity with an IC_{50} value at 20.61 ±0.13 µg/mL (Chen *et al*., 2020).

1.7.3. *Antibiofilm activity*

Leaf and stem ethanol extracts of *R. prinoides* showed significant inhibition of *Staphylococcus aureus* Rosenbach, *Bacillus subtilis* and *Streptococcus mutans* Clarke biofilm formation up to 99.9% and reduced planktonic cell growth up to 10 log units relative to untreated controls(Campbell *et al*., 2019). In a related study, the stem ethanol extracts disrupted *S. mutans* and *C. albicans* co-culture synergism, with 98% less polymicrobial biofilm formation than the untreated control (Campbell *et al*., 2020).

1.7.4. *Antibacterial activity*

Antibacterial activity of methanol and chloroform leaves extracts of *R. prinoides* against *Staphylococcus aureus*, *Streptococcus pyogenes* Rosenbach, *Streptococcus pneumoniae* revealed minimum inhibitory concentration ranging from 8.13-32.5 mg/mL and 8.13-16.25 mg/mL, respectively, compared to a positive control cefotaxin (0.03 mg/mL) and ampicillin (0.01 mg/mL) ranged from 23.67- 28.00 mg/mL in both fractions, respectively (Molla *et al*., 2016).

1.7.5. *Antimalarial activity*

The chloroform root bark extracts of *R.prinoides* were active against chloroquine sensitive *Plasmodium falciparum* strain with IC_{50} value of 3.53 µg/mL (Koch *et al*., 2005). In a related study, *n*-hexane and dichloromethane extracts were demonstrated to have antiplasmodial activity with IC_{50} values of 19.9 µg/mL and 30.3 µg/mL, respectively, with no toxicity in the brine shrimp test (Bosire, 2003). The *in-vitro* antiplasmodial activities of dichloromethane/methanol (1:1) crude extracts and the isolated compounds were performed against the chloroquine-sensitive (D6) and chloroquine-resistant (W2) strains of *Plasmodium falciparum.* The naphthalenic derivative Geshoidin (7) displayed IC_{50} value of 4.0 ± 0.9 pM and 0.4 ± 0.2 pM against the chloroquine sensitive (D6) and chloroquine resistant (W2) strains of *Plasmodium falciparum* (Gebru, 2010). *In vivo* antimalarial activity of aqueous extracts from leaves and root barks against a blood-induced CQ-resistant rodent parasite in mice showed high chemosuppression in the range of 51-75% (Muregi *et al.*, 2007) suggesting the promissing application of leaves, stem bark and roots of *R.prinoides* to treat malaria.

1.7.6. *Antimycobacterial activity*

The acetone leaf extracts of *R.prinoides* demonstrated antimycobacterial activity with minimum inhibitory concentration (MIC) values ranging from 0.625 to >2.5 mg/mL aganist three fast-growing mycobacteria species *i.e. Mycobacterium smegmatis* Trevisan*, Mycobacterium aurum* Tsukamura and *M. fortuitum* Da Costa Cruz and one pathogenic *M. tuberculosis* strain (Dzoyem *et al*., 2016).

1.7.7. *Wound healing activity*

In vivo study in mice revealed that the hydroalcoholic extracts of the leaves of *R. prinoides* possess wound healing activity established by a significant rate of wound contraction and shorter epithelization period. In this study, ten percent of 80% methanol leaves extract showed significant wound contraction against the control and rate increased in significant level with number of days $p < 0.05$, $p < 0.01$, and $p < 0.001$ on days 2 to 4, 8 to 10 and 12 to14, respectively (Tessema *et al.*, 2021). Biological activities of different parts of *R. prinoides* are summerized here below (Table 4).

Table 4. Biological activity of different parts of *R. prinoides*

Plant part	Activity	Reference
Flowers, leaves, stems	Antimutagenic	(Wall *et al*., 1988)
Leaves	Antibacterial	(Chhabra & Uiso, 1991; Chhabra *et al*., 1984; Molla *et al*., 2016)
	Insecticide	(Van Puyvelde et al., 1985)
Root bark	Cytotoxic	(Koch *et al*., 2005)
Leaves, roots, bark root	Antimalarial	(Muregi *et al*., 2007)
Leaves	Wound healing	(Tessema *et al*., 2021)

2. CONCLUSION

The present review presented chemical constituents and biological activity of *R. prinoides* native to Africa and India. Various secondary metabolites such as flavonoids, alkaloids, tannins, terpenoids, saponins, steroids and anthraquinones have been reported from the genus of which polyphenols were abundant with tremedous antioxidant, wound healing and anti-inflammatory activities. Economically, the leaves and stems have been used as hopping agent in the brewery industry, making traditional alcoholic beverages like tella and tej (Ethiopia), animal feed, medicine, nectar for bees, soil conservation, ornamental, and dyes in textiles. Considering diverse class of secondary metabolites as well as wide spectrum of biological activities of the plant, it is believed that plant is a good natural source of polyphenols and can be used as an alternative medicine for future healthcare practice.

Declaration of Conflicting Interests and Ethics

The authors declare no conflict of interest. This research study complies with research publishing ethics. The scientific and legal responsibility for manuscripts published in IJSM belongs to the authors.

Authorship Contribution Statement

GN, MA, SN, FI, YW, MT: literature compilation, review and analysis. **GN & ME**: manuscript write up and review. All authors have read and approved the manuscript.

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