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Traditional uses, phytochemistry and pharmacological uses of *Ruta chalepensis* L: A review

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Abstract
Plants synthesize various secondary metabolites which confers them medicinal properties. Since the time of existence of life, Medicinal plants are used in various systems of medicine such as Ayurveda, Unani, and siddha and in different cultural and religious perspective as well. Nearly 80% of the population in developing countries depend on the traditional knowledge of medicine for treating variety of diseases and disorders. This article reviews the traditional uses, phytochemical composition and pharmacological uses of one such medicinal plant *R. chalepensis* L. of the genus Ruta.

Keywords: Ruta, pharmacology, essential oil, bioactivity, antioxidant, anti-inflammatory

1. Introduction
Ruta chalepensis L., belongs to the family Rutaceae, commonly called ''ruda'' or ''rue'' is a group of small shrub distributed in temperate and tropical countries (Keriman Günaydin & Sezer Savci 2005) [36]. Among 14 species of genus Ruta; R. graveolens and R. chalepensis are available in India and also cultivated in gardens. But these plants should not be touched with bare hands, especially on sunny days (Rubeena Mattummal *et al*. 2018) [55] since the plants of Ruta species are associated with phyto photodermatitis (Gawkrodger DJ and Savin JA. 1983) [26]. These Plants produce a wide variety of secondary metabolite compounds for defense against herbivores, other plants and against microbes. They act as signal compounds as well (Boughendjioua H. 2019) [17].

R. chalepensis is cultivated for its pharmacological and biological activity in many countries, They are used in ethnomedicines, conventional, and complementary alternative medicines as analgesics, anti-inflammatory, antispasmodic, local anesthetic, anthelmintic, antipruritic, and antiseptic and in many other therapeutic uses (Stea *et al*. 2015, Faliagkas *et al*. 2015, T. Markovi´c *et al*. 2016, Jaradat N *et al*. 2016) [20, 44, 34].

2. Materials and methods
A search of the literature on genus *Ruta* and *Ruta chalepensis* was performed using various scientific databases and search engines and the information of articles were reviewed and compiled. An extensive search for literature was made for all the time periods using the genus name "*Ruta"* and the species name "*Ruta chalepensis*". The search was conducted in available online scientific databases such as PubMed, Science Direct, Web of Science and Scopus.

3. Botanical Description
Ruta chalepensis is indigenous to Mediterranean region and Canary Islands, is found growing on rocky places, dry banks and thickets, usually found on limestones and is acclimatized world over (Matu EN 2011) [43]. Rubeena Mattummal *et al*. (2018) [55] have given a clear morphological features of this plant to differentiate it from other Ruta species. According to them, R.chalepensis is a perennial herb grows up to the height of 80 centimeters tall. It has the leaves are grey green color which is 10-12 cm long and 5-8cm broad. Each leaf is divided into several segments which are subdivided into smaller leaflets. The leaflets shape in turn varies from oblong- elliptical to linear with prominent dark spots and oil glands. The strong and unpleasant smell of the plant is attributed to the essential oil present in these leaves which also makes it tastes bitter.

The fruit is a textured capsule which is divided into pointed lobes.

4. Chemical constituents

Ruta chalepensis L is found to be rich in alkaloids, Furocoumarins, coumarins (Günaydin, S. Savci 2005) [36], furoquinolone alkaloids, flavonoids, phenols, amino acids and saponins found in the leaves and young stems of the plant (Hnatyszyn *et al*. 1974) [31]. Studies have also reported terpenoids, tannins, acridone and quinoline along with furanocoumarins, alkaloids, saponins (Mayadah B. *et al*. 2007) [45]. Being an aromatic plant, the plant is rich in essential oils (Nahar, L *et al*. 2021) [48].

Many researchers from different countries have investigated the chemical composition of essential oil present in R.chalepensis including India (Bagchi GD 2003a, 2003 b) [13] and other coutries like Turkey [Baser *et al*. 1996) [14], Greece (O Tzakou and M. Couladis 2001) [64] and Iran (Rustaiyan *et al*. 2002) [56].

Essential oils obtained from the aerial parts of the plant were found to contain predominantly 2-undecanone and 2-nonanone, 2-Dodecanone, 2-Nonanone and 1-Nonene. But variations in the percent composition has been found in the essential oil obtained from different countries (Nidal Jaradat 2017) [49]. This variation can be due to differences in the environmental conditions like quality of the soil, climate changes time of collection and also in method of processing (Nahar, L *et al*. 2021) [48]. Many published studies demonstrated that the yield and chemical composition of the essential oils varied within different geographical areas (Nidal Jaradat 2017) [49].

Boughendjioua H (2019) [17] has reported that 2-undecanone as the chemotype of most essential oils of Ruta species, and hence it serves as a marker of this plant.

5. Traditional uses

The traditional value of Ruta species is evident from their use in Ayurveda, Unani and Siddha medicine. The European Pharmacopoeia includes the various species of this genus.

(Nahar, L.*et al*. 2021) [48] R. chalepensis is used in many countries as traditional medicine in the treatment of a wide variety of diseases. Discords has emphasised this plant for the treatment of nervous diseases (Stuart, 1979) [60].

The decoction of the aerial parts of this plants in Saudi Arabia is used as an analgesic and antipyretic and for the treatment of rheumatism and mental disorders. In Indian system of medicine, the plant is used in the treatment of dropsy, neuralgia, rheumatism and menstrual disorders. The decoction of the roots of this plant is used as an antivenin in Chinese medicine. In Africa, the aqueous decoction of the leaves is used for the treatment of fever. (Mansour S.1990) [41].

R. chalepensis in Jordan is commonly known as Fijin or Sathab and is used in traditional herbal medicine. it also finds use as flavouring agent in food and beverages (Abu-Hamdah, 2001).

In Tunisia the decoction of R. chalepensis is used in the treatment of cultural diseases known as ‘empacho’ (sort of indigestion), ‘mal de ojo’ (evil eye) and for ‘spiritual cleansings’. The plant is used in amulets to confer protection against evil spirits. Also used in various conditions as hysteria, epilepsy, vertigo, colic, intestinal worms, poisonings, headache, anxiety and eye problems. The leaves of this plant infused with vinegar is used in treatment of convulsion and other nervous disorders. In Turkish and Chinese medicines *R. chalepensis* is used as an anti-fertility agent (Khadhri, A., *et al.* 2017) [37].

6. Pharmacological properties

Plants of the family Rutaceae are reported to be having various pharmacological properties *viz*. antibacterial, antifungal, antioxidant, antihelmintic, antitumoral, analgesic, anti-inflammatory, and antidepressant activities (Shorok M. 2018) [9].

6.1 Antioxidant Activity

Study conducted by Nidal Jaradat *et al*. 2017 [49] have reported the antioxidant activity of the essential oil obtained from *R. chalepensis* leaves collected from three Palestinian Regions. The antioxidant potential varied from 69.56%, 61.53% and 24.12% of inhibition potential compared to Trolox a reference antioxidant compound. These variations have been attributed to change in the climate and the soil type which would inturn affect the growth and characteristics of the native flora. The antioxidant activity of methanol/water extract from R.chalepenis is reported to show the antioxidant activity of IC50 = 70.01 μg/ml [D Khlifi *et al*., 2013) [38]

Abdulaziz Y. Al-Ghamdi *et al*. (2020) [1] have reported high antioxidant activity in this plant where scavenging effect ranged between 34.83±11.98% in ethanol extract and 88.13±2.46% in n- butanol extract ($P<0.001$), with the scavenging effect decreasing in the order of n-butanol>ethyl acetate>petroleum ether>chloroform>ethanol. Similar high antioxidant activity of 68.23±0.89 was also reported by Basoudan *et al*. (2019) [15] and Pavi´c *et al*. (2019) [52] with 72.53±0.31% among the extracts studied.

Similar high antioxidant values are reported by Gali and Bedjou, (2018) [25] and Alemayehu *et al*. (2019) [2] at the concentration of 1000 µg/ml used, the scavenging effect of *R. chalepensis* extracts on the DPPH radical which can be attributed to the presence of potent phenolic compounds in R. chalepensis. Medicinal plants containing a wide variety of free radical scavenging molecules such as phenolic compounds, nitrogen compounds, vitamins, terpenoids, and some other endogenous metabolites are rich in antioxidant activity (Zheng and Wang, 2001; Cai *et al*., 2003) [66, 18].

6.2 Antibacterial Activity

The findings of Abdulaziz Y. Al-Ghamdi *et al*. (2020) [1] have showed that the ethanolic extract of R, chalepensis demonstrated antibacterial activity against P. aeruginosa and S. aureus and n-butanol extract was active against B. cereus. Alemayehu *et al*. (2019) [2] reported that methanol, acetone, hexane, and ethyl acetate extracts possess antimicrobial activity against B. cereus, S. aureus, S. typhi and E. coli. Ouerghemmi *et al*. (2017) [50] who found that wild and cultivated Ruta organ extracts showed potent antibacterial activity, with stem extracts effective against S. aureus and P. aeruginosa (16.3 mm and 17.7 mm inhibition zone, respectively) and the cultivated Ruta stem extracts showed the highest antibacterial activity against E. coli. The methanol extract of R. chalepensis leaf at 5 mg/disk displayed a potent inhibiting activity against C. perfringens and E. coli, and no or poor activity against Bifidobacterium bifidum, Bifidobacterium longum, L. acidophilus, and L. casei, while the chloroform extract exhibited a potent activity against C. perfringens and E. coli, whereas butanol

and water extracts showed no activity (Jang-Hee *et al*., 2005) [32].

Methanol extract of R. chalepensis showed MICs of 250 µg/ml and 3.9 µg/ml and induced a maximum of 63% and 94% growth inhibition against S. mutans, as measured by the MTT reduction and CFU methods respectively (Gloria-Garza *et al*., 2013) [27]. Similarly, the acetone extract of R. chalepensis showed maximum inhibition of 8.5 mm against Gram negative bacteria, while ethanol extract showed maximum inhibition against Gram positive bacteria with 8 mm (Babu Kasimala *et al*. 2014) [12]. Alotaibi *et al*. (2018) [5] reported that all the extracts of R chalepensis *viz*; ethanol and collected successive extracts of ether and chloroform, ethyl acetate and n-butanol showed antibacterial activity against all Gram-negative bacteria tested except for Proteus vulgaris and P. aeruginosa.

The highest antibacterial activity of Chalepensis essential oil was observed against Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa and Methicillin Resistant Staphylococcus aureus. Similarly, the essential oil of *Ruta chalepensis* from Jerusalem, Hebron and Jenin regions of Palestine extracted by microwave-ultrasonic method exhibited interesting potential bioactivity against the growth of all microbes examined; Staphylococcus aureus (ATCC 25923), Escherichia coli (ATCC 25922) and Pseudomonas aeruginosa (ATCC 27853) as well as against the growth of a diagnostically confirmed clinical isolates Methicillin Resistant Staphylococcus aureus, MRSA (Jaradat N *et al*. 2017) [49].

6.3 Antifungal activity

In vitro assay of the aerial parts of the ethanol extract of the plant showed good antifungal activity against the strains of dermatophytes particularly against M. canis. Ruta essential oils were reported to possess significant amount of antifungal activity. Both fungicidal and fungi static against various common fungal species, e.g., Alternaria alternata, Aspergillus fumigatus, Aspergillus niger, Candida albicans, and Fusarium oxyxporum (Coimbra, A.T.2020, Haddouchi, F 2013, Saksena, N.1985, Sephavand, A 2018) [19, 30, 57, 58].

The essential oil from R chalepensis demonstrated antifungal activities against Aspergillus Niger, Aspergillus flavus, Alternaria Sp., Trichoderma Sp. and Candida albicans. (Merghache *et al*. 2008) [46].

The essential oil from R chalepensis exhibited significant antifungal activities against Aspergillus Niger, Aspergillus flavus, Alternaria Sp., Trichoderma Sp. and Candida albicans. All three compounds isolated from R chalepensis by Almajmaie *et al*. (2019) [3] were active against the fungal strain Candida albicans.

The phenolic content of the various plant extracts is responsible for the inhibitory effect against bacterial pathogens and in turn these phenolic compounds show their effect by cell membrane adsorption, enzyme interaction, substrate and metal ion deprivation (Ouerghemmi *et al*., 2017) [50].

The plants of the family Rutaceae contains one of the common flavonol glycoside Rutin, which is extensively studies and is established for its antibacterial and antifungal properties (F. Fathiazad *et al*. 2006, M. M. Almutairi *et al*. 2017, DD Orhan *et al*. 2009, RBDQ Pimentel *et al*. 2013) [22, 4, 51, 53].

6.4 Anti-inflammatory properties

The ethanolic extract of R. chalepensis produced significant anti-inflammatory activity against carrageenan-induced paw oedema and cotton pellet granuloma models of inflammation (Mansour *et al*. 1990) [41]. Ethanol and ethyl acetate extracts of R. chalepensis L. showed anti-inflammatory activity against LPS-induced inflammation in RAW 264.7 macrophages (Kacem *et al*. 2015) [35]. The ethanolic extracts of R. chalepensis reduced oxidative stress and inflammation in hypercholesteromic ats (Ashour *et al*. 2011). R. chalepensis L. ethanol and ethyl acetate extracts showed to decrease the COX-2 gene expression, which play a crucial role in mediating inflammatory responses (Fu *et al*. 1990, Mohamed Kacem *et al*. 2014) [47]. *In vitro* assay of *Ruta chalepensis*' oils have exhibited anti-inflammatory activity with edema reduction rate of 53.59% (Khaled Boudjema *et al*. 2018) [16].

6.5 CNS depressant activity

The plant is well known for its depressant activity on the central nervous system (Pollio *et al*. 2008) [54]. A dose-dependent depression of the central nervous system in treated animals was observed in on spontaneous motor activity in mice and conditioned avoidance responding (CAR) in rats (Al-Said MS *et al*. 1990) [6]. The sedative-hypnotic potentiation, anxiolytic, anticonvulsant and antinociceptive effects observed in experimental mice proves that *Ruta chalepensis* induces a depressant activity on the CNS (Gonzalez-Trujano 2005). Ethanolic extract of R. chalepensis exhibited significant dose-dependent CNS depressant activity (Mansour S, *et al*. 1990) [41].

Taiji YOSHIDA (2019) [62] have prepared oral vaccine against Alzheimer's Disease using R. leaves of R. chalepensis since the plant is rich in bioactive compounds that may have synergistic effects with the vaccine for Alzheimer's Disease. M.E. González-Trujano *et al*. 2021 have reported from their experiment that ethyl acetate fraction of R. chalepensis was more efficient than aqueous extract in significantly reducing the incidence of tonic-clinic seizures and mortality in dose-dependent manner in both the PTZ and MES tests. They have concluded that depressant and anticonvulsant effects of R. chalepensis depend in part on the presence of constituents from medium polarity.

6.6 Anticholinesterase inhibitory activity

Sufficient data on the inhibitory effect of *Ruta chalepensis* against AChE and BChE is not available. The inhibition of AChE, the key enzyme in the breakdown of acetylcholine, is considered as one of the treatment strategies against several neurological disorders such as AD, senile dementia, ataxia, myasthenia gravis and constipation. The highest inhibitory activity was exhibited by ethanol extract of R. chalepensis leaves with IC50¼12 ± 1.1 lg/mL (Ayda Khadhri 2017) [11]

Another study by Gali *et al*. 2019 have showed that the chloroform fraction of R. Chalepensis exhibited the most potent activity against AChE and BChE. The butanol extract also showed an efficient anticholinesterase activity that might be due to its flavonoids content. The highest inhibitory effect was exhibited by the alkaloid extract and the results were comparable to that of *galantamine*.

6.7 Anticancer activity

Althaher AR *et al*. (2022) [7] have demonstrated the cytotoxic activity of the R. chalepensis essential oil against human breast cancer cells MCF-7 which can induce apoptosis in a dose and time-dependent manner via an extrinsic caspase-8 dependent pathway. *R.*

chalepensis essential oil as a potential source of the anticancer compound is also suggested by Arwa R. Althaher (2020) [10]. Ethanol extract of the plant exerted a strong cytotoxicity against T-leukemic cells (CEM, H9, Jurkat, and CEM-IRCs) and B lymphoblast cells (SKW 6.4) without affecting normal blood cells, PBL and PBLs (S. Terkmane *et al*. 2018) [63]. Essential oils from R. chalepensis proved to be more toxic to cancerous cells than cells from the established cell line and showed broad as well as cell line specific activity (Andrew Byron Miller *et al*. 2018) [8].

6.8 Anticoagulant activity

Anticoagulant activity of R. chalepensis was showed for all the extracts *viz*; ethanol, ether &chloroform and ethyl acetate & n-butanol at higher concentration with prolonged clotting time 6:30 and 4:30 s at 10 mg/ml concentrations (Shorok M. Alotaibi 2018) [9]. Four phenolic compounds were isolated from the *Ruta chalepensis* which might be responsible for the anticoagulant activity (Ferhat *et al*., 2014, Haddouchi *et al*., 2013) [23, 21].

7. Conclusion

From the above studies, it can be concluded that R chalepensis plant has long been used as traditional medicine worldwide. R. chalepensis, is a potential source of natural bioactive molecules. This plant is used in traditional herbal medicine in many countries for treatment of a wide variety of diseases. Topically it is used as hair tonic, insect repellent and for snakebite and also used as a flavouring agent in food and beverages.

Number of research studies have showed the bioactive potential of phytochemicals from *R. chalepensis.* However further research is needed on the mechanism of action of the Phytochemical compounds to clarify their bioefficacy as well as feasibility for commercial drug formulation.

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