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## Ruta graveolens: from Traditional System of Medicine to Modern Pharmacology: an Overview

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### ABSTRACT

The family of Rutaceae contains extremely wide variety of aromatic plants, mainly in tropical regions. Among them the rich is the genus *Ruta*. It is now cultivated in many parts of the world. This plant is considered indigenous in South Europe and North Africa and it grows on waste stony ground. Rue (*Ruta graveolens*) has been used for centuries as a medical preparation and has a variety of roles, probably because of its varied chemical composition. This plant is commonly cultivated in India and is commonly called as sudab or sadab. In traditional system of medicine it is used as stimulant, emmenagogue, diuretic, abortefacient, and resolvent. Detailed and comparative studies from its traditional use especially with reference to Unani system of Medicine, to the modern scientific reports have been evaluated in this paper.

**Keywords:** Sudab; *Ruta graveolens*; Unani system of Medicine; Flavonoid.

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## INTRODUCTION

The family of Rutaceae contains extremely wide variety of aromatic plants, mainly in tropical regions. Among them the rich is the genus *Ruta*.<sup>1</sup> It is now cultivated in many parts of the world. This plant is considered indigenous in South Europe and North Africa and it grows on waste stony ground.<sup>2-4</sup> The Rutaceae is one of the largest plant families with approximately 150 genera and 1,500 species distributed largely in tropical and subtropical parts of the world.<sup>5</sup> This family is known throughout the world for its citrus fruits such as oranges, lemons and grape fruit and also called as citrus family.<sup>6</sup> A variety of plants of the family Rutaceae are used in traditional system of medicine world-wide. The most common medicinal plant of this family is *Ruta graveolens* L., which is commonly known as 'Rue' or 'Sudab' or 'Sadab' in Hindi (Indian language). Although it is native to Europe, it is distributed throughout the world. It is an ornamental evergreen shrub of up to one meter tall and has considerable medicinal importance. More than 120 natural compounds mainly including acridone alkaloids, coumarines, essential oils, flavonoids, and furoquinolines have been found in the roots and aerial parts of this plant,<sup>7</sup> and is the main source of furanocoumarins such as psoralen, xanthotoxin (8-methoxy-psoralen; 8-MOP) and bergapten (5-methoxy-psoralen; 5-MOP).<sup>8</sup>

This plant is commonly cultivated in India and is commonly called as sudab or sadab.<sup>2,4,9</sup> Two species of *Ruta* (genus) are reported to grow in India, of which *Ruta graveolens* (garden rue) is well known for its aromatic and medicinal uses.<sup>4</sup> In traditional system of medicine it is used as stimulant, emmenagogue, diuretic, and abortifacient, resolvent.<sup>2-4,9-14</sup>

It is a perennial herbaceous or half-shrubby plant, reaching 2 to 2 1/2 feet in height, with a strong, heavy and unpleasant smell. Fruits are dry, hard rounded, 4 or 5 lobed at the top grayish-brown and rough. Seeds are ovoid, rounded on the back, flattish in front, angular, testa blackish, rough; embryo slightly curved from the base to the apex and is surrounded by scanty fleshy endosperm.<sup>9,13</sup>

### Vernacular Names

Hindi: Sanool, Saatri; Urdu: Sudab; Arabic: Sudab, Suzab; Persian: Satap; Greek: Fejan, Safayan; Sanskrit: Sadapah; English: Rue, Garden Rue, Herb of grace.<sup>2,4,10,11,15</sup>

## PHARMACOLOGICAL ACTIONS IN TRADITIONAL AND ETHNO MEDICINE

Almost in all the traditional medicine, the medicinal plants play an important role and constitute the backbone for the same. A comparative view between the pharmacological actions mentioned

in the traditional system of medicine especially in the Unani system and in the modern botanists in their books is given below. The relevance in the actions of both the medicines shows the accuracy of the data. This comparison provides a brief summary that the traditional system of medicines itself has lot of experienced evidences not a mere of serendipity.

Actions mentioned in Unani system of medicine	Actions mentioned in Ethno medicine
1. <i>Mulattif</i> (Demulcent) <sup>16</sup>	1. Resolvent <sup>4,13,17-20</sup>
2. <i>Mufattehe sudab</i> (Anti-thrombotic/Anti-embolic/Deobsruent) <sup>10,11,15</sup>	2. Stimulant <sup>4,13,14,18,21,22</sup>
3. <i>Musakhkhin</i> (Calorific/Calorifacient) <sup>10,15,23</sup>	3. Rubefacient <sup>4,9</sup>
4. <i>Muhallil</i> (Resolvent) <sup>10,11,15,16,23,24</sup>	4. Emmenagogue <sup>4,9,25</sup>
5. <i>Mudirre baul wa haiz</i> (Diuretic and Emmenagogue) <sup>10,11,15,24</sup>	5. Diuretic <sup>4,9,25,26</sup>
6. <i>Musqite janeen</i> (Abortefacient) <sup>11</sup>	6. Abortefacient <sup>4,13,22</sup>
7. <i>Muhallile riyah</i> (Carminative) <sup>10,11,15,23,27</sup>	7. Anthelmintic <sup>4,17,18</sup>
8. <i>Muqawwie dimagh</i> (Brain Tonic) <sup>11,28</sup>	8. Antispasmodic <sup>4,13,18,19,21,29</sup>
9. <i>Muqawwie meda</i> (Stomachic) <sup>11,15</sup>	9. Tonic and Digestive <sup>9,17,25,26</sup>
10. <i>Mushtahi</i> (Appetizer) <sup>11,15,27,28</sup>	10. Antiepileptic <sup>4,19</sup>
11. <i>Mujaffife mani</i> (Desiccant of semen) <sup>10,11,16,23,24,28</sup>	11. Vermifuge <sup>9,29</sup>
12. <i>Qaate bah</i> (Anaphrodisiac/Antaphrodisiac) <sup>10,11,24</sup>	12. Anaphrodisiac <sup>13,18</sup>
13. <i>Mufattite sange gurda wa masana</i> (Lithotripitic) <sup>11</sup>	
14. <i>Muqawwie basar</i> (Increase Eyesight) <sup>10</sup>	
15. <i>Manae hamal</i> (Anti-conceptive) <sup>11,28</sup>	
16. <i>Mujaffif</i> (Desiccant/Siccative) <sup>10,24</sup>	
17. <i>Qabiz</i> (Astringent) <sup>10</sup>	

#### Medicinal uses in Traditional medicine

1. The local use of this drug along with honey is a good treatment for paralysis, tremors, joint pain and nervine disorders.<sup>30,27</sup>
2. The decoction of *Sudab* when used as enema relieves colitis, flatulence and flatulent colitis.<sup>11,10,28</sup>
3. Being an analgesic, it's useful in the chest pain caused by pneumonia and pleurisy. It is also useful in dyspnoea, sciatica, gout, arthritis and flatulent colic.<sup>11,24</sup>
4. The local application of paste of *Sudab* leaves, on the abdomen is effective in dropsy.<sup>11,10,28</sup>
5. The infusion of *Sudab* leaves is used as nasal drop to treat the infantile paralysis.<sup>11</sup>
6. The drug is useful in the disorders of kidney, urinary bladder and helps regulate the function of these organs. It also relieves the back pain and chest pain.<sup>11,30,10,28</sup>
7. According to Jalinoos (Galen) the use of *Sudab* is perfect treatment for epilepsy and antidote of various poisons.<sup>10,28</sup>

8. The tincture of the *Sudab* leaves with or without salt in appropriate quantity improves the eyesight.<sup>10</sup>
9. *Sudab* leaves are used as suppository or as tampon for extravaginal application or given orally in the form of syrup in case of amenorrhea. It helps in expulsion of fetus and placenta.<sup>11</sup>
10. It strengthens the eye-sight specially when its extract is taken orally or used as *Kohl* (stibium) along with the extract of fennel and honey.<sup>30,27</sup>
11. The powdered seeds of this drug are abortefacient.<sup>11,12</sup>
12. It has litholytic properties against the renal and vesicular calculi.<sup>11,30,28</sup>

**Formulations in Unani system:** Safoof Sailanurrehm, Jawarish Kamooni, Majoone Halteeth.<sup>12</sup>

### Medicinal uses in Ethno medicine

The herb and the oil act as stimulants, their influences being chiefly directed to the uterine and nervous system.<sup>13,2</sup>

It's a valuable diuretic<sup>13,2,9,31,17,18</sup>

It is applied locally in the treatment of rheumatism of joints, feet, lions.<sup>4</sup> In Punjab; the leaves are used as a remedy for rheumatic pains.<sup>13</sup>

Rue is chiefly used to encourage the onset of menstruation. It stimulates the muscles of uterus and promotes menstrual flow.<sup>20,14</sup> The plant is used as an emmenagogue in India and China.<sup>13,14,29</sup>

Rue in all forms is considered as injurious to pregnant women.<sup>13</sup> It is found to be powerful anaphrodisiac and abortefacient to pregnant women.<sup>13,9</sup> It causes uterine haemorrhage and inflammation of uterus.<sup>18</sup> The drug produces pain in the back, bearing down and frequent micturition, followed by pain and abortion about ten days after the commencement of its administration. This plant has strong antispasmodic properties. The juice undoubtedly possesses antispasmodic and expectorant properties. The spasmolytic property of the herb is attributed to the presence of coumarins and also the essential oil.<sup>13,4</sup>

In European herbal medicine, rue has also been taken to treat conditions as varied as epilepsy, vertigo, poisoning and eye problems. Infact for the eye problems, an infusion is used as eyewash, brings quick relief to strained and tired eyes and reputedly improves the eyesight.<sup>20</sup>

### Agrochemical effects

1. Efficacy of rue extract, sodium bicarbonate and fungicides activity was done on tobacco leaves to control powdery mildew of tobacco. The efficacy of hydrolic extract of leaves of *Ruta graveolens* showed biological activity on conidia of *E. orontii* and provided a

good disease control up to 90%. Rue extract was also very effective for controlling powdery mildew in repeated application. Infact, the Bupirimate (fungicide) reduced the disease severity to a level equivalent to that attained with rue extract, requiring two applications to obtain its maximum effectiveness.<sup>31</sup>

2. Fungicide; in vitro fungistatic activity of rue (*Ruta graveolens*) extract against six species of fungus has been evaluated earlier. Seven compounds were found to have moderate to good activity against plant pathogenic fungi that are problems with horticultural crops. Special bioassay directed isolation technique for these compounds were done from the leaves of *Ruta graveolens*.<sup>32,33</sup>

## CHEMICAL CONSTITUENTS

The chemical constituents present include rutin (2%), imperatorin, isoimperatorin, xanthotoxin, bergapten, psoralen. The alkaloids graveoline, gravelinine, rutamine, rutamarine, are also present in the herb.<sup>13,9,4</sup> Analysis of seeds gave following values; nitrogenous substances 21.6%, fixed oil 36.8%, and ash 13.8%. The oil from seeds is of drying type (iodine value; 189) and its fatty acid composition is as; palmitic acid 21.8%, stearic acid 9.1%, oleic acid 22.0% and linoleic acid 44.5%. The unsaponified matter contains ceryle alcohol, sitosterol and new coumarins.<sup>4</sup> The pure oil of rue consists of 90% of methyl nonyleketone. This plant also contains glucoside rutin.<sup>13</sup>

The flavonoids are a part of primary chemical components of *Ruta graveolens* Linn. The most important analyzed flavonoids are rutin (quercetin-3- $\beta$ -rutinoside) that belongs to flavonol glycoside. Quercetin is other major flavonoids found in *Ruta graveolens* and can also be obtained by rutin hydrolysis.<sup>34</sup>

*Ruta graveolens* plants accumulate linear furanocoumarins (psoralens) and acridone or furoquinolone alkaloids. The acridone alkaloids were detected in all organs particularly in endodermal and vascular tissues.<sup>35,36</sup>

### New extraction techniques

New extraction techniques for alkaloids of *Ruta graveolens* along with other two drugs, *Hyocymus muticus* and *Datura stramonium* were done by use of a sonicating solution containing surfactant as extracting agent. The results show that the presence of surfactant enhances the amount of total alkaloid extracted even at low concentration. The concentration of surfactant required to extract the alkaloid is directly related to the alkaloid content of the drug.<sup>37</sup>

### Pharmacognostical and Phytochemical Standardization

Pharmacognostical standardization of aerial parts of *Ruta graveolens* reveals that highest extract in successive extraction by aqueous extract followed by methanolic extract. Saponins were absent in all extractions. The pH of aqueous extract was 6.74.<sup>38</sup> The physicochemical, phytochemical and HPLC studies of seeds of the *Ruta graveolens* also showed highest extractive value in hydro alcoholic extract ( $3.40 \pm 0.61$ ) followed by aqueous ( $2.37 \pm 0.33$ ) and alcoholic extracts ( $2.25 \pm 0.53$ ). HPLC reveals the presence of 3 and 7 major chemical constituents in isocratic and gradient elution series respectively.<sup>39</sup>

### Side Effects

Rue is an acro-narcotic poison. When fresh its tropical action is acrid and if much handled it produces redness, swelling and even vesication.<sup>2,4,13,18</sup>

It is an active irritant whether applied externally or taken internally; sometimes it produces painful vomiting, always great prostration, and confusion of mind, cloudy vision, feebleness and slowness of pulse, coldness of extremities and twitching of the limbs.<sup>3</sup>

Allergic reactions have been reported by common rue (contact dermatitis) and photodermatitis.<sup>4,19,40</sup>

### Hepatotoxicity:

The effect of low levels of dietary 10% leaves of *Ruta graveolens* and 10% leaves *Solenostemma argel* or their mixture on Bovans chicks was studied. A depression in growth and hepatotoxicity characterized were noticed on feeding them separately the leaves. Hepatotoxicity, widespread congestion and hemorrhage in chicks fed *Ruta graveolens* leaves alone were marked and accompanied by anemia and decrease in serum concentrations of total protein, albumin, globulin, cholesterol, and other serum constituents. Feeding the mixture of the two plants caused more marked depression in growth but no death among the chicks occurred.<sup>41</sup>

## MODERN SCIENTIFIC REPORTS

### Medicinal properties

#### 1. Anti-oxidant Activity:

1. Inhibitory effects of 70% methanolic extract of leaves of *Ruta graveolens* on Guinea pig liver aldehyde oxidase enzyme shows 89-96% inhibition. Total extract as well as the major flavonoids of *Ruta graveolens*, Quercetin and Rutin both are able to inhibit the hepatic aldehyde oxidase activity, which was in a dose dependent manner. The inhibitory effect of Quercetin on the enzyme was found to be more potent than menadione, the known specific inhibitor of aldehyde oxidase<sup>42</sup>

## 2. **Anti-inflammatory Activity:**

Methanolic extract of *Ruta graveolens* with a concentration of 20 mg/kg and ethanolic extract with a concentration of 50 mg/kg showed maximum (90.9%) inhibition on carrageenan induced paw edema in wistar male rats. The effect was significantly higher than that of the standard drug Diclofenac sodium (72.72%).<sup>43,44</sup>

## 3. **Anti-inflammatory and Anti-oxidant Activity:**

Anti-inflammatory and anti-oxidant effects of methanolic extract of *Ruta graveolens* L. in adjuvant induced arthritis in rats were studied. Methanolic extract of *Ruta graveolens* exhibited maximum percentage of edema inhibition at a dose of 20 mg/kg on 21st day of adjuvant arthritis. The effect was higher than that of standard drug indomethacin. The activities of cyclooxygenase-2 and myeloperoxidase and concentration of thiobarbituric acid reactive substance (TBARS) were decreased and the activities of antioxidant enzymes, vitamins C & E and reduced glutathione level were increased on treatment with methanolic extract of *Ruta graveolens*.<sup>43-45</sup>

## 4. **Cytotoxic Activity on Human Cancer Cell:**

Investigation of cytotoxic activity on human cancer cell lines of arborinine and furanoacridones isolated from *Ruta graveolens*. The compounds were applied in vitro to three types of human cancer cells: MCF-7 (breast adenocarcinoma), HeLa (cervix adenocarcinoma) and A431 (skin epidermoid carcinoma). Doxorubicin and cisplatin were used as positive controls. Arborine displayed the highest antiproliferative effects. Compounds 3, 4, 5 and 7 also displayed significant antiproliferative effects.

The effects of compounds 3, 4 and 7 were examined more closely. Staining of the cell cultures revealed that the application of the compounds to HeLa cells resulted in typical morphological features of apoptosis, including increased cell membrane permeability, cellular shrinkage and granulation in the nucleus.

When cell cultures were examined for the proportion of apoptotic cells, they were found to increase in a dose dependant manner. Compounds 3 and 7 increased apoptosis most significantly. The mRNA ratio of Bax/Bcl-2 (markers of apoptosis) was also dose dependently increased.<sup>46</sup>

## 5. **Anti-tumour Activity:**

Anti-tumor activity of *Ruta graveolens* extract was found to be cytotoxic to Dalton's lymphoma ascites (DLA), Ehrlich ascites carcinoma (EAC) and L929 cells in culture (IC<sub>100</sub>=16 mg/ml) and also to increase the lifespan of tumour bearing animals. The

extract decreased solid tumours developing from DLA and EAC cells when given simultaneously with elongation of the lifespan of tumour-bearing animals. The extract was found to scavenge hydroxyl radicals and inhibit lipid per oxidation at lower concentrations but the effect was minimal on higher concentration.<sup>47</sup>

**6. Anti-arrhythmic Activity:**

Alkaloidal extract of *Ruta graveolens* in isolated rat hearts shows a potential anti-arrhythmic effect. Extracts of *Ruta graveolens* significantly prolongs effective and functional refractory periods and nodal conduction time in a rate dependent manner and the effects of the extract appears on both the slow and fast pathways of the node.<sup>48</sup>

**7. Anti-oxidative Activity:**

Various extracts of *Ruta graveolens* and *Citrus sinensis* were investigated for the inhibition of the oxidation of L-DOPA catalysed by mushroom tyrosinase and correlated activity with the content of phenolic compounds and its cytotoxicity.<sup>49</sup>

**8. Antimicrobial and Cytotoxic Activities:**

The methanol, petroleum ether, ethyl acetate and water-methanol extracts of *Ruta graveolens* were found to possess antimicrobial and cytotoxic activities.<sup>50</sup>

9. An alcoholic extract of the herb shows antibacterial activity against *Micrococcus pyogenes* var. *aureus* and *Escherichia coli*.<sup>4</sup>

10. Psoralen present in this herb produce marked spasmolytic effect on isolated rabbit ileum.<sup>4</sup>

11. The combined effects of two aqueous extracts of *Viola odorata*, and the *Ruta graveolens*, with concentrations on the growth of *Trichomonas vaginalis* was carried out. The results showed that there is a variation of inhibition in different concentrations of two extracts and complete inhibition was seen with a concentration 10 mg/cm<sup>3</sup> for 48 hrs.<sup>51</sup>

**12. Anti-androgenic Activity:**

Anti-androgenic activity of *Ruta graveolens* in male albino rats with emphasis on sexual and aggressive behaviour was done which reveals decrease in sperm motility and density in cauda epididymis and testicular ducts. Decreased spermatogenic activity was observed in somniferous tubules, testosterone and FSH levels were found decreased and aggressive behaviour was also diminished.<sup>52</sup>

**13. Anti-conceptive and Anti-fertility Activity:**

The anti-conceptive and anti-fertility of various *Ruta graveolens* extracts were tested in Sprague-Dawley adult female rats. The administration of different extracts significantly increased the number of resorbed embryos. There was no significant effect on maternal

weight gain, but some extracts showed a significant reduction in fetal weight. Administration of Hexane extract on post-coitum significantly decreased the number of females with born fetuses and increased the mortality rate among the born foetuses.<sup>53</sup>

14. Ethanolic extracts of *Ruta graveolens* and *Cannabis sativa* in adult Wistar male rats showed significant reduced spermatogenesis. The effect of *Ruta graveolens* was more than *Cannabis sativa*. Both the drugs showed significant reduction in the epididymal sperm counts.<sup>42</sup>

15. Immobilization effect of aqueous extract of *Ruta graveolens* on human sperm was carried out at different doses. The sperm immobilization effects of the extract appeared immediately in a dose-dependent manner and 100% of the sperms became immotile at a concentration of 100 mg/ml.<sup>54</sup>

### Modern Pharmacology

The phytochemical investigations of the *Ruta graveolens* have demonstrated the presence of flavonoids, rutin, quercetin, furocoumarin and lemonins as its major active constituents.<sup>4,9</sup> The most important analyzed flavonoids are rutin (quercetin-3- $\beta$ -rutoside) and quercetin.<sup>42</sup> Rutin and quercetin have been reported to possess anti-inflammatory, anti-oxidant, anti-thrombotic and superoxide scavenger properties.<sup>55,56,57,58</sup> Besides these, several essential oils have been reported in *Ruta graveolens* having anti-inflammatory and cytotoxic properties.<sup>46,47,43, 47, 59, 60</sup>

Flavonoids exhibit several biological effects such as anti-inflammatory, antihepatotoxic and anti-ulcer actions. They also inhibit enzymes such as aldose reductase and xanthine oxidase.<sup>61</sup> They are potent antioxidants and have free radical scavenging activities. Many have anti-allergic, antiviral actions and some of them provide protection against cardiovascular mortality.<sup>62</sup> They have been shown to inhibit the growth of various cancer cell lines in vitro, and reduce tumour development in experimental animals.<sup>63</sup>

### CONCLUSION

*Ruta graveolens* occupies an important place in traditional systems of medicine especially in Unani and Homeopathic medicines. So far more than 120 natural compounds mainly including acridone alkaloids, coumarines, essential oils, flavonoids, and furoquinolines have been discovered. In modern pharmacology, the major active constituents flavonoids, rutin, quercetin, furocoumarin and lemonins play an important role and a "lead" as a natural substance in various diseases and inflammatory conditions and for many synthetic drugs.

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