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Potential Usage of *Ruta graveolens* L. in Ophthalmology

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A B S T R A C T

Objective: There has been growing interest in medicinal plants due to their therapeutic properties in safe lower doses, despite their unpleasant smell, bitter taste, and toxicity in higher doses. *Ruta graveolens* L., commonly known as the herb of grace, common rue, rue, ruda, sodab, fijen, and al-suzab is a potential therapeutic candidate with variable healing properties and traditional uses. One of its lesser-known uses is in the treatment of eye conditions. The current study aimed to investigate the ophthalmological potential of *Ruta graveolens* L. using available scientific literature.

Methods: To this end, we extensively searched Scopus, Science Direct, Web of Science, Embase, PubMed, Google Scholar, IranMedex, SID, and Magiran for related literature on the cultural, historical and scientific aspects of *Ruta graveolens* L. and ophthalmology. Also, traditional Persian medicine books including Al-Qanun Fi Al-Tibb, Al-Hawi Fi Al-Tibb, Al-Abniya, and Ikhtiyarat Badiei thoroughly searched to find the potential application of rue in ophthalmology.

Results: Our historical, literary, and traditional medicine data revealed that *R. graveolens* L. used in the ophthalmic field probably due to its beneficial effects in the past. Also, there are some modern studies elucidated the beneficial effects of this plant in ophthalmology.

Conclusion: This study suggests that *R. graveolens* L. plant can be a promising ophthalmic drug due to its specific ocular benefits warranting further research with modern technologies.

Keywords: Integrative Medicine, Medicinal plant, Pharmacology, Persian Medicine, Ophthalmology, *Ruta graveolens* L

➢ **How to cite this paper**

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Introduction

Medicinal plants attract the attention of many researchers throughout the history of pharmacy due to their variable therapeutic activities in smaller doses. Their popularity is growing daily all over the world due to the major complications and side effects of conventional medicine. As a result, there has been significant scientific progress in exploring the potential benefits of medicinal plants [1].

Ruta graveolens L. (*R. graveolens* L.) is a potential candidate belongs to family Rutaceae. It is also known as the herb of grace, common rue, rue, ruda, or sadab (also known as sodab, satap, or fijen in Persian, or al-suzab in Arabic). This medicinal herb is cultivated or grows wildly and is used in different traditional medical systems for a variety of ailments. It has a peculiar minty pungent smell and bitter taste. While used as a digestive, tonic, and aphrodisiac in small doses, it is irritant in larger doses. However, the novel characteristics of this therapeutic plant have been identified, such as its resistance to mutagenesis and DNA strand breaks.

R. graveolens L. has also been demonstrated to increase the susceptibility of cancer cells to death while having no effect on normal cells by inducing the removal of an amide group from the antiapoptotic protein Bcl-xL in human brain cancer cells but not in healthy B and T lymphocytes [2,3]. Anciently, *R. graveolens* L. was also used as spices in some cultures and is considered as a sacred plant in some rites [4]. William Shakespeare mentioned this plant in the play *Richard* III [5]. The aim of the present study is to evaluate literature-based evidence for *R. graveolens* L. ophthalmological applications.

Materials and methods

This study was a narrative review using a queried keywords composed of R. graveolens L., herb of grace, common rue, rue, ruda, sodab, satap, fijen, sadab, and al-suzab as well as ophthalmology, eye, and treatment by extensive research on online available data. We used databases including Scopus, Science Direct, Embase, Web of Science, PubMed, Google scholar, SID, IranMedex, and Magiran. After trying our best to evaluate those validated publications in English and Persian in line with our research subject at the initial phase, the subject-oriented studies read and scrutinized carefully to extract and present the relevant data in our study while we strictly avoided predatory publications. Moreover, to elucidate the potential usage of rue in ophthalmology, traditional Persian medicine books including Al-Qanun Fi Al-Tibb, Al-Hawi Fi Al-Tibb, Al-Abniya, and Ikhtiyarat Badiei extensively probed using keywords of R. graveolens L. herb of grace, common rue, rue, ruda, sodab, sadab, fijen, al-suzab, ophthalmology, eye, and treatment in Arabic and Persian.

Results

R. graveolens L. is a perennial herb (Figure 1.), and according to folk belief, is used as a sacred plant to reduce eye pain [4]. Our examination on the literature related to the historical and cultural aspects also showed that *R. graveolens* L. is used in the field of ophthalmology due to its special medicinal benefits for the eye. Historically, the famous ophthalmologist William Holland Wilmer (1863–1936 AD) who was named the Wilmer Eye Institute of the Johns Hopkins University School of Medicine for his contribution to the field of ophthalmology, mentioned in an article that the famous English writer and poet John Milton (1608–1674 AD), who suffered from eye disease, was a proponent of using *R. graveolens* L. as an ophthalmic drug.

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Figure 1. A: *Ruta. graveolens* L., white and black image. Adapted from: W. Woodville, Medical botany: https://jstor.org/stable/community.24742187. **B:** *Ruta. graveolens* L., colored image. Adapted from: Rowan, M., *R. graveolens* L. (rue): https://jstor.org/stable/community.24807794.

He mentioned it in his masterpiece "Paradise Lost". After his death, researchers speculated on the etiology of his visual disorder, based on his biography and statements in literary works, on various disorders ranging from myopia to ocular tumor or chronic glaucoma, and even though we could not find out the exact cause [6], this at least suggests that knowledge about the ophthalmic effects of this plant has passed down from ancient times to the 17th century.

Our results show that the beneficial effects of *R. graveolens* L. for eye diseases are also well documented in the traditional Persian medical textbooks, which recommends to use this herb as an oral or topical drug [7]. Persian scholars such as Ibn Sina (Avicenna) (980–1037 AD) in his book Al-Qanun Fi Al-Tibb (the Canon of Medicine), Rhazes (Abū Bakr Muhammad ibn Zakariyyā Rāzī also known as Al-Razi or Razi) (865–925 AD) in his book Al-Hawi Fi Al-Tibb (The Comprehensive Book on Medicine), Abu Mansur Muwaffaq ibn Ali al-Harawi (Heravi) (10th AD) in his book Al-Abniya (Al Abnieh an Haghaiegh al Advieh or Rawḍat al-uns wa-manfaʿat al-nafs, also transliterated in English as The principles of the real character of medicinal plants), and Ali ibn Hosein Ansari Shirazi also known as Haji Zain al-Attar (1330–1404 AD) in his book Ekhtiyarat i Badi'i (Ikhtiyarat Badiei) addressed the ophthalmological application of *R. graveolens* L. (Table 1).

Table 1. Ophthalmological application of rue (*Ruta graveolens* L.) mentioned in different traditional Persian medicine books.

Name of scholar	Traditional Persian medicine textbook	Application of rue (fijen, al-suzab) in ophthalmology	Ref.
Ibn Sina (Avicenna) (980-1037 AD)	Al-Qanun Fi Al-Tibb (the Canon of Medicine)	Rue and especially its plant juice, which is mixed with fennel plant juice and honey and applied to the eyes or eaten, strengthens vision. If make a dressing of rue and put it on the eyes, it will stop the throbbing and inflammation of the eyes. If make a salve from rue, fennel, myrrh, and honey and rub it around the eyes, it will remove the blurred vision.	[15]
Rhazes (Abū Bakr Muhammad ibn Zakariyyā Rāzī also known as Al-Razi or Razi) (865–925 AD)	Al-Hawi Fi Al-Tibb (The Comprehensive Book on Medicine)	Rue is useful for different ailments including eye disease. The consequence of eating too much rue is bulging of the eyes, burning, and inflammation	[16]
Abu Mansur Muwaffaq ibn Ali al-Harawi (Heravi) (10th AD)	Al-Abniya (Al Abnieh an Haghaiegh al Advieh or Rawḍat al-uns wa-manfaʿat al-nafs, also transliterated in English as The principles of the real character of medicinal plants)	If a mixture of rue and Angabin (honey) put on the eye, it will increase the vision.	[17]

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Ali ibn Hosein Ansari Shirazi (Haji Zain al-Attar) (1330–1404 AD)	Ekhtiyarat i Badi'i (Ikhtiyarat Badiei)	If it wears as a kohl, it will increase the brightness of eyes. Eating too much of it is harmful to the eyes	[18]

Moreover, our result disclosed that the side effects of this plant on the eye, or in other words its ocular toxicity, when an excessive amounts used, were well-recognized in traditional Persian medicine sources in such a way that Persian scholars mentioned this matter in their medical books in medieval times. For example, Rhazes, a renowned Persian physician of medieval times, suggested the beneficial effects of rue (*R. graveolens* L.) for eye diseases, and at the same time warned physicians about the toxic effects of overconsumption of *R. graveolens* L. that can be resulted in the bulging, burning, and inflammation of eyes in the poisoned patient [8]. This protrusion of the eyes which may be considered today as equivalent to exophthalmos or proptosis, as well as the burning and inflammatory features of the *R. graveolens* L. can be attributed to the matter of the ocular orientation of *R. graveolens* L. exerting its pharmacological and toxicological effects on the eyes.

Discussion

The present study tried to accumulate and analyze the currently available scientific evidence on the potential usage of *R. graveolens* L. in ophthalmology. Collectively, our historical, cultural, and experimental data showed that there are a promising ophthalmological properties for *R. graveolens* L. However, the question is whether there are specific receptors associated with the structures and functions of the eye in such a way that *R. graveolens* L. exerts its ophthalmic effects via their interaction and modulations. And what are the chemical compounds of the plant that can affect the structures or functions in the ocular system. In fact, *R. graveolens* L. has many different chemical constituents (Table 2.). However, there is a lack of research that can be inferred that what chemical compounds of the *R. graveolens* L. can be attributed to its ophthalmological properties. Also, current literate did not address the ophthalmological efficacy and safety of *R. graveolens* L.

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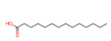
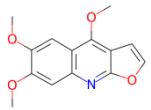
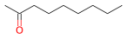
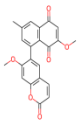
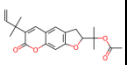
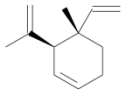
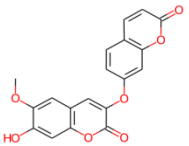
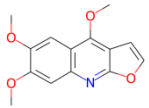
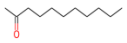
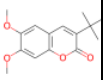
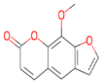
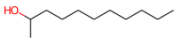
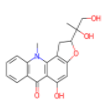
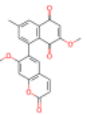
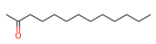
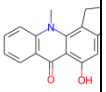
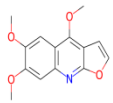
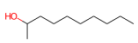
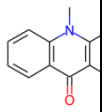
Leaf		Aerial part		Flower		Fruit		Root		Whole plant	
Phytochemical name	Chemical structure	Phytochemical name	Chemical structure	Phytochemical name	Chemical structure	Phytochemical name	Chemical structure	Phytochemical name	Chemical structure	Phytochemical name	Chemical structure
Myristic acid		Kokusaginine		Hexadecane		2-Nonanone		Naphthoherniarin		Rutamarin	
Geijerene		Daphnoretin		Kokusaginine		2-Undecanone		Rutacultin		Methoxsalen	
Isophytol				2-Undecanol				Gravacridonediol		Naphthoherniarin	
Hexadecane				2-Tridecanone				Rutacridone		Coumarin	
Kokusaginine				2-Decanol				Gravacridonetriol		Pangelin	

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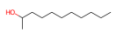
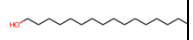
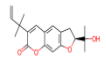
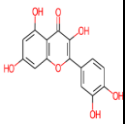
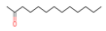
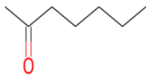
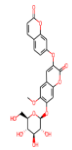
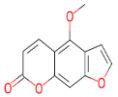
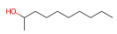
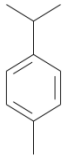
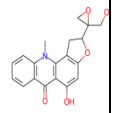
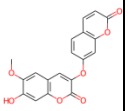
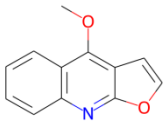
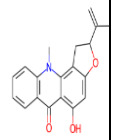
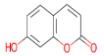
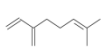
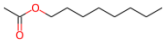
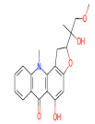
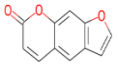
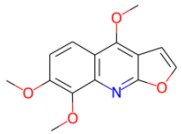
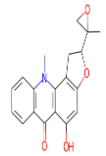
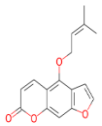
2-Undecanol				1-Hexadecanol				Chalepin		Quercetin	
2-Tridecanone				2-Heptanone				Daphnorin		Bergapten	
2-Decanol				p-Cymene				20-Hydroxyrutacridone epoxide		Daphnoretin	
1-Hexadecanol				Dictamnine				Gravacridonol		Umbelliferone	
Myrcene				Octyl acetate				Gravacridonediol methyl ether		Psoralen	
Nonanal				Skimmianine				Rutacridone epoxide		Isoimperatorin	

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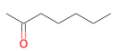
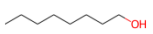
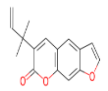
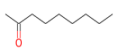
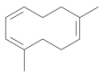
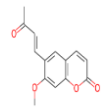
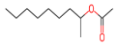
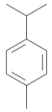
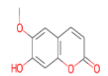
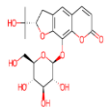
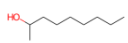
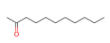
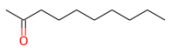
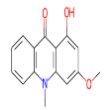
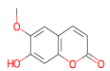
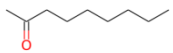
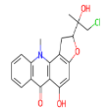
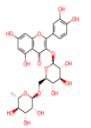
2-Heptanone				1-Octanol				Chalepensin		2-Nonanone	
Pregeijerene				1-Pentadecanol				Suberenone		1-Methyloctyl acetate	
p-Cymene				Tridecane				Scopoletin		Rutarin	
Psoralen				2-Nonanol				1-Hydroxy-10-methylacridone		2-Undecanone	
Decanal				2-Decanone				1-Hydroxy-3-methoxy-10-methylacridone		Scopoletin	
1-Tetradecanol				2-Nonanone				Isogravacridonechlorine		Rutin	

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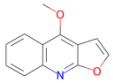
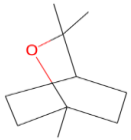
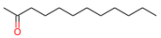
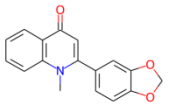
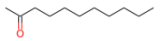
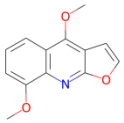
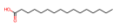
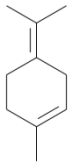
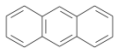
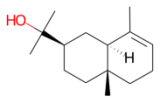
Dictamnine				Eucalyptol							
2-Octanone				2-Dodecanone							
Dodecanal				Graveoline							
Octyl acetate				2-Undecanone							
Skimmianine				gamma-Fagarine							
Palmitic acid				Terpinolene							
Anthracene				alpha-Eudesmol							

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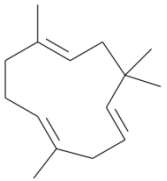
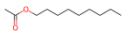
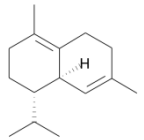
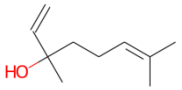
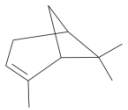
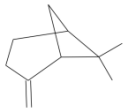
1-Octanol				Humulene							
Nonyl acetate				(+)-delta-Cadinene							
1-Undecene				Linalool							
1-Pentadecanol				alpha-Pinene							
Heptadecane				beta-Pinene							
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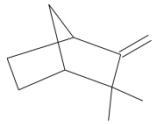
Tridecane				**Camphene**							

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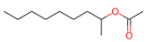
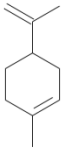
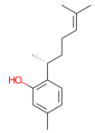
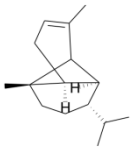
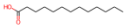
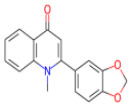
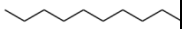
1-Methyloctyl acetate				**Limonene**							
Curcuphenol				**alpha-Copaene**							
Tridecanoic acid				**2-Nonene**							
Graveoline				**Dodec-2-ene**							

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We want to encourage an extra analysis of the outcomes of the usage of *R. graveolens* L. and its constituents on the structures and functions of the eyes. Also, there is a demand for a well-designed validated studies such as randomized controlled trials (RCTs) to decipher the potential efficacy and safety of *R. graveolens* L. for potential ophthalmological applications.

Our current understanding is that *R. graveolens* L. contains a variety of active chemicals including flavonoids, alkaloids, and furanocoumarins, and has various pharmacological properties such as anti-inflammatory, anti-allergic, antimicrobial, antifungal, antioxidant, and anticancer activities just to name a few. As Table 2 presented the details of pharmacologically active ingredient of *R. graveolens* L, any of these chemicals may be attributable for ophthalmological properties.

Even though some photoreactive ingredients of *R. graveolens* L. can cause severe inflammation, phytophotodermatitis, and associated skin injuries in high doses [9], it has been suggested that the chemical compounds such as 8-methoxy psoralen (xanthotoxin; methoxsalen) and 5-methoxy psoralen (bergapten) can be used in photodynamic therapy while applied in small, adjusted doses [10].

R. graveolens L. contains several alkaloids such as rutin, graveoline, and graveolinine. Recent research has shown that rutin, as one of the compounds in this plant, can prevent the occurrence of cataracts by inhibiting the formation of glycation end products in the lens proteins of the eyes in animal models. Studies have also showed that rutin reduces eye pressure [11].

An interesting recent study revealed the inhibitory effects of R. graveloens L. water extract on the cell growth and angiogenesis through modulation of signaling pathways of MEK-ERK1/2 inside cells [12]. Also, a pilot study showed the promising effects of this plant on the ocular dysfunction due to multiple sclerosis and attributed its mechanism to the potassium channel blocking as a result of the effects of psoralens analogues ingredients present in the plant [13]. There is also a report on the effects of *R. graveolens* L. on delaying the progression of myopia [14].

Conclusion

Conclusively, this work suggests potential ophthalmological effects for *R. graveolens* L. by presenting different evidence from historical, cultural, and experimental aspects as well as some supportive modern literature that warranting further research towards ophthalmological drug discovery from chemical compounds of *R. graveolens* L. by using modern, state-of-the-art tools and technologies. Also, more reliable studies including RCTs needed to assess the potential efficacy and toxicity of *R. graveolens* L. for future ophthalmological utilizations.

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