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REVIEW

Traditional Uses, Phytochemistry, Pharmacology and Toxicology of *Ruta graveolens L.*: A Critical Review and Future Perspectives

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Abstract: Medicinal plants are fundamental sources of natural products with high chemical diversity and specificity as novel lead compounds with diverse pharmacological activities. *Ruta graveolens L.* is an important traditional Chinese medicine used to treat fever caused by cold, wind-fire toothache, headache, bruises and sprains, irregular menstruation, and infantile eczema. Although various traditional uses and chemical constituent activity evaluations have been reported, no systematic review and future perspective of *R. graveolens* has been published. A total of 113 literature about *R. graveolens* were collected from online scientific databases, including SciFinder, PubMed, CNKI, Web of Science, and Google Scholar. Additional information was obtained from other sources of literature, such as the Chinese Pharmacopoeia, Flora of China, classical Chinese herbal books and local prints and scripts. Herein, we comprehensively review the traditional uses, phytochemistry, pharmacology, and toxicology of *R. graveolens*, and provide critical comments and meaningful perspectives for the future development of this medicinal plant.

Keywords: *Ruta graveolens*, traditional use, chemical constituents, pharmacological properties, toxicology

Introduction

Medicinal plants exhibit important biological activities and are an important source of research and development of small molecule new drugs, such as *kalanchoe pinnata, Artemisia annua* Linn., *Glycyrrhizae Radix* et Rhizoma., *Rhodiola crenulate*.[1–10] *Ruta graveolens L.* (rue) is a shrubby perennial plant of the Rutaceae family that originated in the Mediterranean region and was brought to Mexico and tropical America from Spain.[11] *R. graveolens* is now cultivated worldwide, including in Europe and many African, Asian, and South American countries such as Ethiopia, China, and Japan.[12,13] The word *graveolens* comes from Latin and means strong smelling; a strong unpleasant odor emanates from the plant's leaves, hence the name. *R. graveolens*, also called "Chou Cao", is a smelly herb. The flavor is very bitter, although it is used in ethnic cuisines such as a coffee flavoring in Ethiopia, a milk tea flavoring in Guangdong province in China, and to flavor grappa, an Italian type of brandy.[14,15]

The official name of *R. graveolens* in Chinese is Yun Xiang, and its folk names include Chou Cao, Xiao Xiang Cao, Jin Jie Qi and Xiang Cao. Dried or fresh whole plants of *R. graveolens*, including roots, stems, and leaves, are used in traditional Chinese medicines to remove heat and toxic materials, disperse stasis, and relieve pain.[16] Over the past few decades, extensive chemical analyses and modern activity evaluations have been conducted to validate its traditional uses. Phytochemical studies have profiled 231 compounds including alkaloids (acridone, quinolones, and quinolines), phenylpropyl (simple phenylpropyl and furanocoumarins), flavonoids, steroids, anthraquinones, volatile oils, and other active components.[17,18] These active constituents are the material basis for the antibacterial, anti-inflammatory, anti-oxidative stress, anticancer, antiproliferative, fertility-regulating, and antiviral activities of *R. graveolens*, as well as their pharmacological effects on the nervous and cardiovascular systems. Some studies have described the phototoxicity of *R.*

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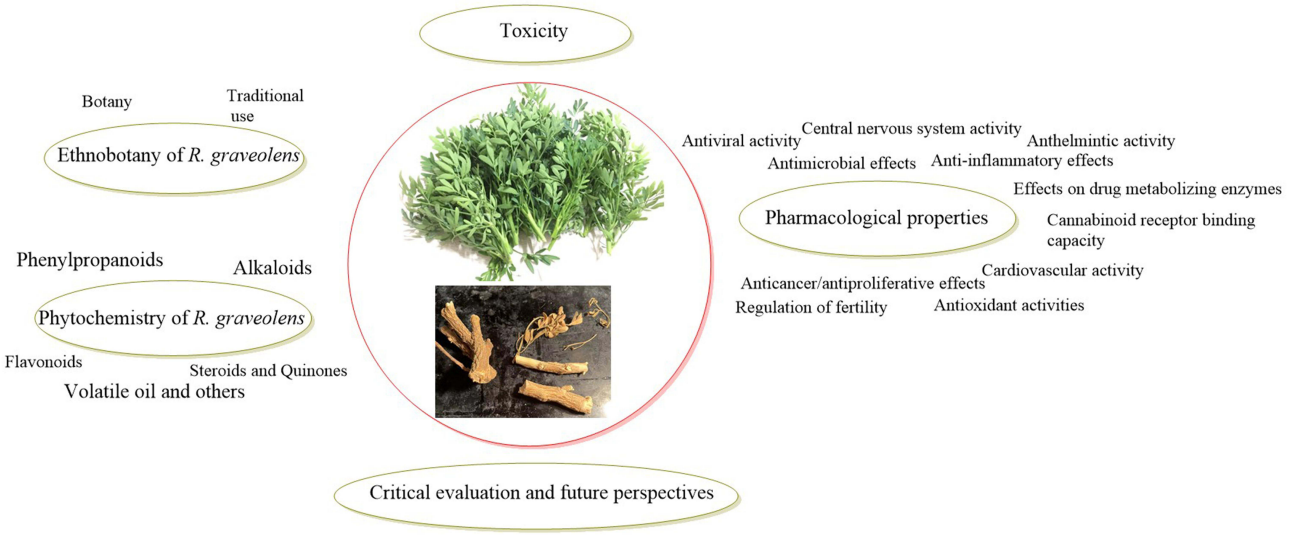
Graphical Abstract



graveolens and its toxicity in pregnant women,[19,20] but toxicity assessment of the constituents of *R. graveolens* remains insufficient. To evaluate the efficacy and safety of *R. graveolens*, this systematic review describes and provides future perspectives on its traditional use, phytochemistry, pharmacological effects, and toxicity. This will provide a solid foundation for the comprehensive development of drugs based on *R. graveolens*, and their clinical efficacy and safety.

Ethnobotany of R. graveolens

Botany

R. graveolens is a perennial herbaceous evergreen dicot shrub belonging to the Rutaceae family. The plant is glabrous and glandular, and emits a strong and distinctive scent. The plant can reach heights of up to 1 m. It has pinnately compound leaves, featuring two to three pairs of leaflets measuring 6–12 cm in length. The terminal leaflet is typically short, spatulate, or narrowly elliptic, ranging from 5 to 30 mm in length and 2–5 mm in width, with a gray-green or slightly bluish-green hue. The flowers display a vibrant golden yellow color and have a diameter of ~2 cm. The calyx comprises four lobes and four petals. There are eight stamens, with four initially attached to the petals upon blooming, while the remaining four are angled and exposed opposite to the sepals, gradually elongating to align with the length of the fully bloomed flowers. The pistil is short, and the ovary typically contains four chambers, each housing numerous ovules (see Figure 1 for plant morphology). The fruit measures between 6 and 10 mm in length, split from the top to the middle, with raised oil glands on the skin. The plentiful seeds are kidney-shaped, ~1.5 mm long, and dark brown in color. The flowering period extends from March to June, and late winter, with fruit ripening occurring from July to September.[16,21,22] *R. graveolens* prefers warm and humid climates and is more widely distributed in temperate and tropical areas but is tolerant of cold and drought. Native to Southern Europe and North Africa, where it often grows on abandoned stony land, it is now distributed worldwide and cultivated in both North and South China.

Traditional Use

R. graveolens is widely used in food, cosmetic, and pharmaceutical industries. Owing to its aromatic, antioxidant, and antimicrobial activities, *R. graveolens* is used as a flavoring agent and fragrance in food, perfumes, and cosmetics. It is also cultivated as a landscape plant because of its attractive foliage. The most noteworthy application of *R.* graveolens, however, is traditional medicine, in diverse cultures worldwide. In countries such as Iran, it is known as the "cure-all" because of its broad therapeutic range, including anti-parasitic, analgesic, and anti-inflammatory effects, and its use in

Figure 1 Plant morphology of *R. graveolens*..

gynecological disorders.[23–26] In Latin American folk medicine, it is the most important drug used to induce abortions. In traditional Chinese medicine, *R. graveolens* is slightly bitter, pungent, flat, and cool and belongs to the lung, kidney, liver, and heart meridians. It has the effect of clearing away heat and detoxifying the toxin, cooling the blood and dispersing blood stasis, and it can be used for treating colds and fevers, rheumatism and paralysis, pediatric fevers and convulsions, feverish sores and canker sores, insect and snake bites, amenorrhea and abortion, as well as eczema and other skin disorders.[12] The medicinal value of *R. graveolens* is recorded in many ancient books in China and has been variously described as "eliminating hundred poisons, dispersing big sores, managing snake wounds" (Sheng Cao Yao Xing Bei Yao), "irregular treatment of amenorrhea, colic pain" (Chinese Medicine Planting Guide), "smelly grass leaves, either raw or boiled, treat diarrhea and urinary obstruction" (Gang Mu Shi Yi), and "fresh smelly grass stems, leaves (10–15g) and mung bean (15 g) are soaked in boiling water to treat children eczema" (Fujian Chinese Herbal Medicine). Although many traditional uses have been reported, the efficacy of *R. graveolens* for these indications needs to be studied and validated using modern pharmacological methods.

Phytochemistry of R. graveolens

More than 200 compounds have been identified in *R. graveolens*. In this study, 92 papers were reviewed, and 231 chemical constituents were identified (see Figures 2–5 for structures). In addition, numerous volatile oil components have been reported in *R. graveolens*, which produce its strong and unique odor. The compounds in the non-volatile fraction of *R. graveolens* are mainly phenylpropanoids, especially coumarins and alkaloids, and predominantly acridone and quinoline alkaloids. Flavonoids are less present in the plant and feature in fewer papers, and the least abundant non-volatile components are steroids and quinones.

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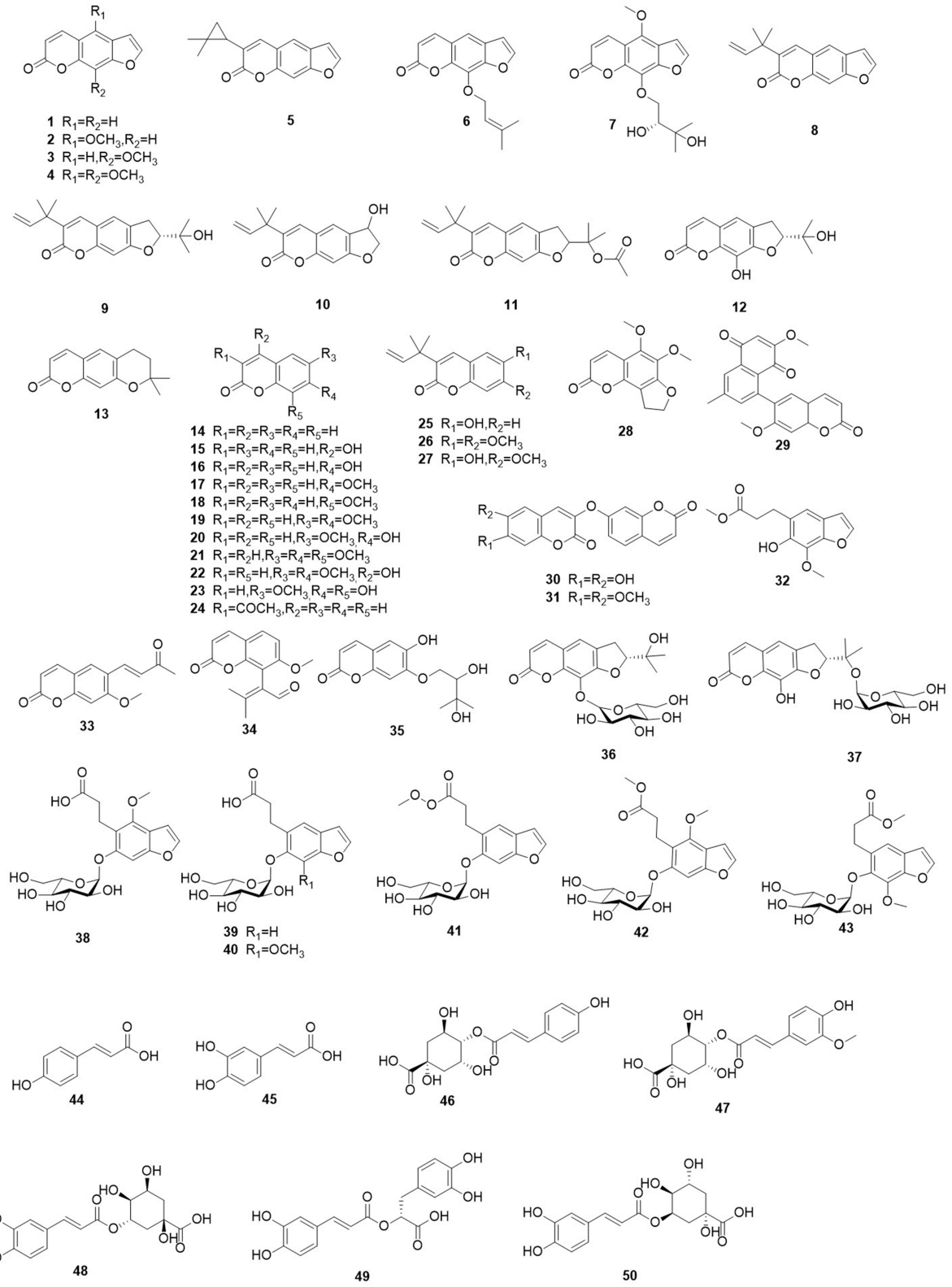

Figure 2 Structures of phenylpropanoids in *R. graveolens*..

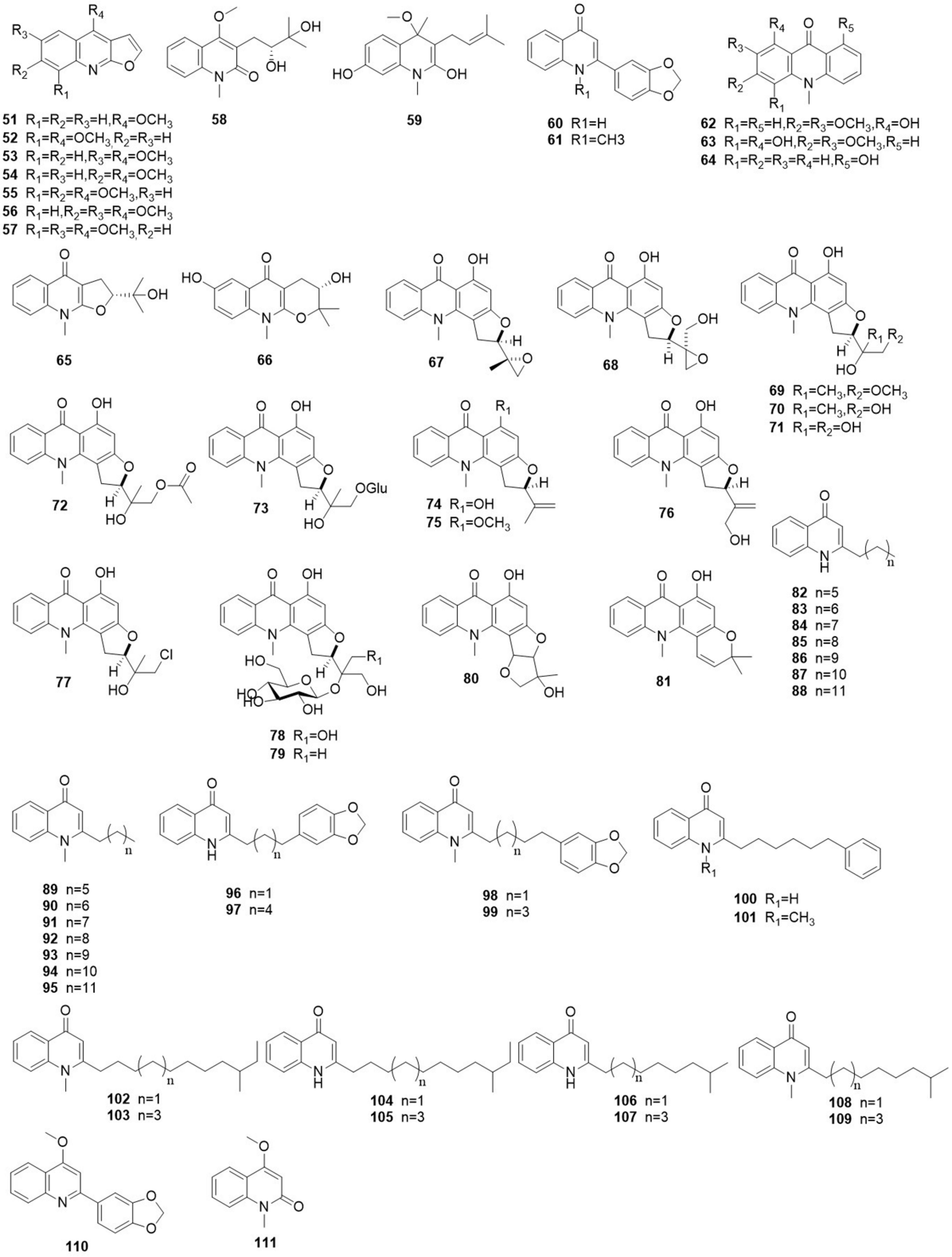

Figure 3 Structures of alkaloids in *R. graveolens*..

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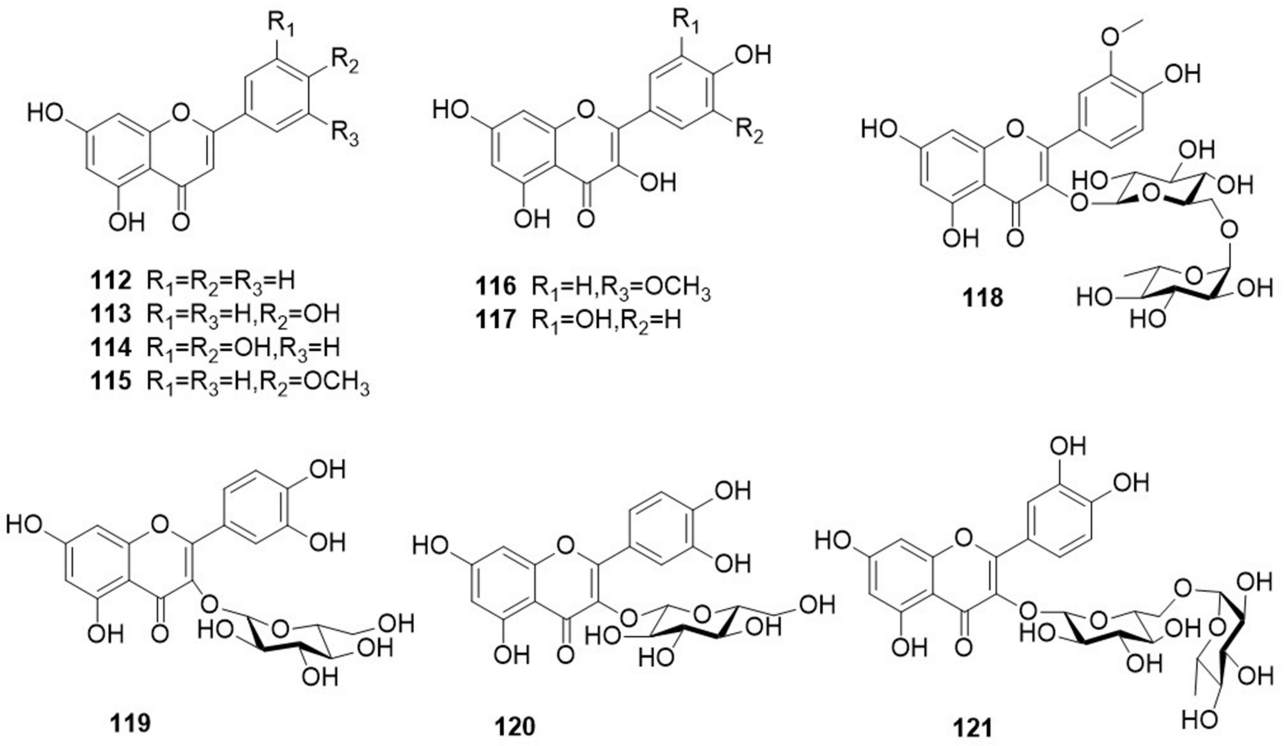

Figure 4 Structures of flavonoids in *R. graveolens*..

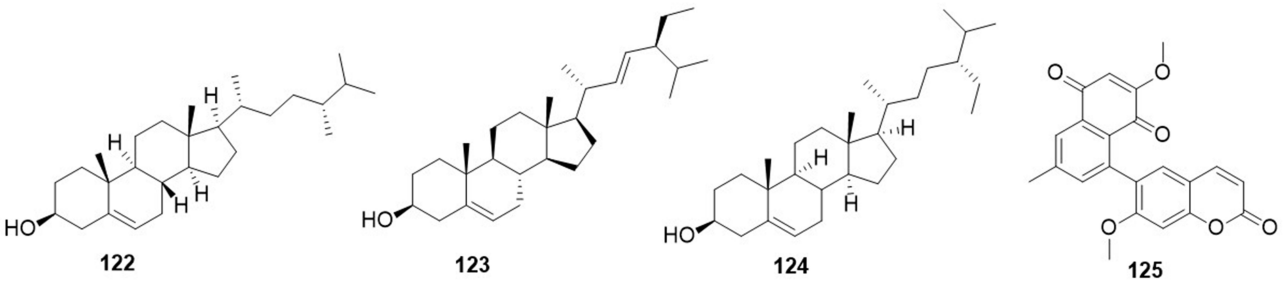

Figure 5 Structures of steroids and quinones in *R. graveolens*..

Phenylpropanoids

Phenylpropanoid constituents are abundant in *R. graveolens* and 43 such compounds are reviewed in this paper (Table 1, Figure 2). They include simple phenylpropanoids, furanocoumarins, coumarins, and lignans. Compounds 1–12, 28, 36, and 37 are furanocoumarins; compound 13 is a pyranocoumarin; compounds 14–27, 29–31, and 33–35 belong to the other coumarin groups; compounds 32 and 38–43 are lignans; and compounds 44–50 are phenylpropanoids.[19,20,27–48] However, the structure of some compounds requires comprehensive spectral verification and, for coumarins containing chiral carbon centers, stereochemical analysis is required to determine their configurations.

Alkaloids

Alkaloids are the most abundant non-volatile chemical components in *R. graveolens*, of which acridone alkaloids are the most frequently reported, followed by quinoline alkaloids. A total of 61 alkaloidal constituents isolated from *R. graveolens* were reviewed (Table 2, Figure 3). Among them, compounds 51–59 and 65 are furan quinoline alkaloids,

Table 1 Chemical Constituent of Phenylpropanoids in R. graveolens

No.	Compounds	Chemical Formula	References
Phenylpropanoids			
Furanocoumarin			
1	Psoralen	$C_{11}H_6O_3$	[27]
2	Bergapten	$C_{12}H_8O_4$	[28]
3	Xanthotoxin	$C_{12}H_8O_4$	[29]
4	Isopimpinellin	$C_{13}H_{10}O_5$	[28]
5	Clausindin	$C_{16}H_{14}O_3$	[27]
6	Imperatorin	$C_{16}H_{14}O_4$	[28]
7	Byakangelicin	$C_{14}H_{14}O_5$	[30]
8	Chalepensin	$C_{19}H_{22}O_4$	[27]
9	Chalepin	$C_{22}H_{24}O_3$	[31]
10	3-(2",2"-dimethyl butenyl)3-hydroxydihydrofuropsoralen	$C_{17}H_{18}O_4$	[32]
11	Rutamarin	$C_{21}H_{24}O_5$	[27]
12	Rutaretin	$C_{14}H_{14}O_3$	[33]
28	Pimpinellin	$C_{13}H_{12}O_5$	[19]
36	Rutarin	$C_{20}H_{24}O_{10}$	[20]
37	Isorutarin	$C_{20}H_{24}O_{10}$	[20]
Pyranocoumarin			
13	Xanthyletin	$C_{16}H_{14}O_3$	[30]
Other coumarins			
14	Coumarin	$C_9H_6O_2$	[34]
15	4-Hydroxycoumarin	$C_9H_6O_3$	[35]
16	7-Hydroxycoumarin	$C_9H_6O_2$	[36]
17	7-Methoxycoumarin	$C_{10}H_8O_3$	[37]
18	8-Methoxycoumarin	$C_{10}H_8O_3$	[38]
19	6,7-Dimethoxycoumarin	$C_{11}H_{10}O_4$	[34]
20	Scopoletin	$C_{10}H_8O_4$	[27]
21	6,7,8-Trimethoxycoumarin	$C_{12}H_{12}O_5$	[37]
22	6,7-Dimethoxy, 4-metylocoumarin	$C_{12}H_{12}O_4$	[34]
23	7,8-Dihydroxy, 6-metoxycoumarin	$C_{10}H_8O_5$	[34]
24	3-Acetylcoumarin	$C_{11}H_8O_3$	[34]
25	3-(1,1-dimethyl-allyl)6-hydroxy-chromen-2-one	$C_{14}H_{14}O_3$	[39]
26	Rutacultin	$C_{16}H_{18}O_4$	[34]
27	3-(1′-1′-dimethyl-allyl)-6-hydroxy-7-methoxy-coumarin	$C_{15}H_{16}O_4$	[40]
29	Naphthoherniarin	$C_{22}H_{18}O_6$	[41]
30	Daphnoretin methyl ether	$C_{18}H_{10}O_7$	[37]
31	O-methyl-daphnoretin	$C_{20}H_{14}O_7$	[42]
33	Suberenone	$C_{14}H_{12}O_4$	[43]
34	Murralongin	$C_{15}H_{14}O_4$	[44]
35	Rutaretin	$C_{14}H_{16}O_6$	[45]
Phenylpropanoic acid			
32	Methyl-3-(6-hydroxy-7-methoxybenzofuran-5-yl) propanoate	$C_{13}H_{14}O_5$	[37]
38	Picraquassioside A	$C_{18}H_{22}O_{10}$	[46]
39	Cnidioside A	$C_{17}H_{20}O_9$	[20]
40	Cnidioside B	$C_{18}H_{22}O_{10}$	[20]
41	Methylcnidioside A	$C_{18}H_{22}O_{10}$	[46]
42	Methylpicraquassioside A	$C_{19}H_{24}O_{10}$	[46]
43	Methyl ester	$C_{19}H_{24}O_{10}$	[20]
Phenylpropene			
44	p-Coumaric acid	$C_9H_8O_3$	[47]
45	Caffeic acid	$C_9H_8O_4$	[47]

(*Continued*)

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Table 1 (Continued).

No.	Compounds	Chemical Formula	References
46	4-o-Feruloylquinic acid	$C_{16}H_{18}O_8$	[48]
47	4-o-p-Cumaroylquinic acid	$C_{17}H_{20}O_9$	[48]
48	Chlorogenic acid	$C_{16}H_{18}O_9$	[47]
49	Rosmarinic acid	$C_{18}H_{16}O_8$	[47]
50	Isochlorogenic acid	$C_{16}H_{18}O_9$	[47]

Table 2 Chemical Constituent of Alkaloids in R. graveolens

No.	Compounds	Chemical Formula	References
Alkaloids			
Furaquinoline alkaloids			
51	Dictamnine	$C_{12}H_9NO_2$	[49]
52	*γ*-fagarine	$C_{13}H_{11}NO_3$	[28]
53	Ptelein	$C_{13}H_{11}NO_3$	[49]
54	Evolitrine	$C_{13}H_{11}NO_3$	[50]
55	Skimmianine	$C_{14}H_{13}NO_4$	[27]
56	Kokusaginine	$C_{14}H_{13}NO_4$	[49]
57	4,6,8-Trimethoxyfuro[2,3-*b*]-quinoline	$C_{14}H_{13}NO_4$	[49]
58	Edulinine	$C_{16}H_{21}NO_4$	[37]
59	(4*S*)-1,4-Dihydro-4-methoxy-1,4-dimethyl-3-(3-methylbut-2-enyl)-quinoline-2,7-diol	$C_{17}H_{23}NO_3$	[51]
64	1-Hydroxy-10-methylacridone	$C_{14}H_{11}NO_2$	[27]
Acridone alkaloids			
62	Arborinine	$C_{16}H_{15}NO_4$	[27]
63	1,4-Dihydroxy-2,3-dimethoxy-10-methylacridin-9(10*H*)-one	$C_{16}H_{15}NO_5$	[52]
65	Isoplatydesmine	$C_{15}H_{17}NO_3$	[37]
67	Rutacridonepoxide	$C_{19}H_{17}NO_4$	[53]
68	20-Hydroxyrutacridone epoxide	$C_{19}H_{17}NO_5$	[53]
69	Gravacridonediol monomethyl ether	$C_{20}H_{21}NO_5$	[54]
70	Gravacridondiol	$C_{19}H_{19}NO_5$	[55]
71	Gravacridonetriol	$C_{18}H_{17}NO_6$	[55]
72	Gravacriondiolacetate	$C_{21}H_{21}NO_6$	[55]
73	Gravacridondiol glucoside	$C_{25}H_{29}NO_{10}$	[56]
74	Rutacridone	$C_{19}H_{17}NO_3$	[55]
75	(*R*)-5-Methoxy-11-methyl-2-(prop-1-en-2-yl)-1,11-dihydrofuro[2,3-*c*]-acridin-6(2*H*)-one	$C_{20}H_{19}NO_3$	[53]
76	Gravacridonol	$C_{19}H_{17}NO_4$	[53]
77	Isogravacridone chlorine	$C_{19}H_{18}ClNO_4$	[57]
78	Gravacridontriol glucoside	$C_{25}H_{29}NO_{11}$	[58]
79	Gravacridonediol glucoside	$C_{25}H_{29}NO_{10}$	[59]
80	Rutagravin	$C_{19}H_{17}NO_5$	[53]
81	Acronycins	$C_{19}H_{17}NO_3$	[60]
Quinolone alkaloids			
82	2-Heptyl-4(1*H*)-quinolone	$C_{16}H_{21}NO$	[29]
83	2-Octyl-4(1*H*)-quinolone	$C_{17}H_{23}NO$	[29]
84	2-Nonyl-4(1*H*)-quinolone	$C_{18}H_{25}NO$	[29]

(*Continued*)

Table 2 (Continued).

No.	Compounds	Chemical Formula	References
85	4-Hydroxy-2-decylquinoline	$C_{19}H_{27}NO$	[31]
86	4-Hydroxy-2-undecylquinoline	$C_{20}H_{29}NO$	[31]
87	2-Undecyl-4(1*H*)-quinolone	$C_{21}H_{31}NO$	[31]
88	2-Tridecylquinolin-4(1*H*)-one	$C_{22}H_{33}NO$	[61]
89	Schinifoline	$C_{17}H_{23}NO$	[61]
90	1-Methyl-2-octylquinolin-4(1*H*)-one	$C_{18}H_{25}NO$	[61]
91	1-Methyl-2-nonyl-4(1*H*)-quinolone	$C_{19}H_{27}NO$	[62]
92	1-Methyl-2-decyl-4(1*H*)-quinolone	$C_{20}H_{29}NO$	[31]
93	1-Methyl-2-undecyl-4(1*H*)-quinolone	$C_{21}H_{31}NO$	[29]
94	1-Methyl-2-dodecyl-4(1*H*)-quinolone	$C_{22}H_{33}NO$	[29]
95	Dihydroevocarpine	$C_{23}H_{35}NO$	[31]
96	2-[4′ (3′,4′-Methylenedioxyphenyl) butyl]-4-quinolone	$C_{19}H_{17}NO_3$	[61]
97	1-Methyl-2-[6′(3′,4′-methylenedioxyphenyl) hexyl]-4-quinolone	$C_{22}H_{23}NO_3$	[61]
98	2-(4-(Benzo[*d*][1,3]-dioxol-5-yl)-butyl)-1-methylquinolin-4(1*H*)-one	$C_{21}H_{21}NO_3$	[63]
99	2-(6-(Benzo[*d*][1,3]-dioxol-5-yl)-hexyl)-1-methylquinolin-4(1*H*)-one	$C_{23}H_{25}NO_3$	[63]
100	2-(6-Phenylhexyl)-quinolin-4(1*H*)-one	$C_{21}H_{23}NO$	[61]
101	1-Methyl-2-(6-phenylhexyl)-quinolin-4(1*H*)-one	$C_{22}H_{25}NO$	[61]
102	1-Methyl-2-(9-methylundecyl)-quinolin-4(1*H*)-one	$C_{22}H_{33}NO$	[61]
103	1-Methyl-2-(11-methyltridecyl)-quinolin-4(1*H*)-one	$C_{24}H_{37}NO$	[61]
104	2-(9-Methylundecyl)-quinolin-4(1*H*)-one	$C_{21}H_{31}NO$	[61]
105	2-(11-Methyltridecyl)-quinolin-4(1*H*)-one	$C_{23}H_{35}NO$	[61]
106	2-(7-Methyloctyl)-quinolin-4(1*H*)-one	$C_{18}H_{25}NO$	[61]
107	2-(9-Methyldecyl)-quinolin-4(1*H*)-one	$C_{20}H_{29}NO$	[61]
108	1-Methyl-2-(7-methyloctyl)-quinolin-4(1*H*)-one	$C_{19}H_{27}NO$	[61]
109	1-Methyl-2-(9-methyldecyl)-quinolin-4(1*H*)-one	$C_{21}H_{31}NO$	[61]
111	4-Methoxy-1-methylquinolin-2(1*H*)-one	$C_{11}H_{11}NO_2$	[52]
Other alkaloids			
60	Graveoline	$C_{17}H_{15}NO_3$	[27]
61	Norgraveoline	$C_{16}H_{11}NO_3$	[27]
66	Ribalinidine	$C_{15}H_{17}NO_4$	[37]
110	Graveolinine	$C_{17}H_{13}NO_3$	[37]

compounds 62–64 and 67–81 are acridone alkaloids, compounds 82–109 and 111 are quinolone alkaloids, and compounds 60–61, 66, and 110 belong to other alkaloid groups.[27–29,31,37,49–63]

Flavonoids

Flavonoids are an important class of plant secondary metabolites that have a wide range of biological activities. Ten flavonoids reported in *R. graveolens* are reviewed in this study (Table 3, Figure 4). Among them, compounds 112–115, 118, and 119 are flavones and compounds 116–117, 120, and 121 are flavonols.[48,64–66]

Steroids and Quinones

Steroids are a class of natural product components with cyclopentanoperhydrophenanthrene parent nuclei that play an important role in plant life processes. Steroids are less described among the reported chemical constituents of *R. graveolens* (Table 3, Figure 5), this paper details a total of three steroidal chemical constituents, compounds 122–124.[67] Quinones are a class of compounds with unsaturated cyclic diketone structures and diverse biological activities, with anthraquinone compounds being the most abundant. Only one quinone isolated from *R. graveolens* was reviewed in this study (Table 3): anthraquinone 125.[41]

Table 3 Chemical Constituent of Flavonoids, Steroids and Quinones in R. graveolens

No.	Compounds	Chemical Formula	References
Flavones			
112	Chrysin	$C_{15}H_{10}O_4$	[64]
113	Naringenin	$C_{15}H_{12}O_5$	[64]
114	Luteolin	$C_{15}H_{10}O_6$	[65]
115	Acacetin	$C_{16}H_{12}O_5$	[48]
118	Narcissoside	$C_{28}H_{32}O_{16}$	[65]
119	Isoquercetin	$C_{21}H_{20}O_{12}$	[64]
Flavonol			
116	Isorhamnetin	$C_{16}H_{12}O_7$	[66]
117	Quercetin	$C_{15}H_{10}O_7$	[65]
120	Hyperoside	$C_{21}H_{20}O_{11}$	[65]
121	Rutin	$C_{27}H_{30}O_{16}$	[65]
Steroids			
122	Campasterol	$C_{28}H_{48}O$	[67]
123	Stigmasterol	$C_{29}H_{48}O$	[67]
124	β-sitosterol	$C_{29}H_{50}O$	[67]
Anthraquinone			
125	7-Methoxy-6-(5,8-dioxo-7-methoxy-3-methyl-5,8-dihydronaphthalen-1-yl)-chromen-2-one	$C_{15}H_{10}O_4$	[41]

Volatile Oil and Others

Many volatile oil compounds, including phenolic acids, terpenoids, and esters, have been identified in the Rutaceae family. In addition to volatile oils, fatty acids and other components have been identified. A total of 113 volatile oils and other chemical components identified in *R. graveolens* were reviewed (Table 4, Figure 6).[30,37,47,49,65,67–79]

Pharmacological Properties

R. graveolens presents diverse pharmacological activities, the most commonly reported of which are its antibacterial and anti-inflammatory effects. Anticancer, antiproliferative, antioxidant, fertility-regulating, antiviral, and anthelmintic properties are also well documented, as well as their effects on the nervous system (Figure 7). In addition to activity studies on its single constituents, many reports have described activity studies on the extracts of *R. graveolens*, of which

Table 4 Chemical Constituent of Volatile Oil and Others in R. graveolens

No.	Compounds	Chemical Formula	References
126	Cyclohexene	C_6H_{10}	[68]
127	1,2,3-Trimethylcyclohexane	C_9H_{18}	[69]
128	2-Methylphenol	$C_7H_8O_2$	[70]
129	2-Methoxy-4-vinylphenol	$C_9H_{10}O_2$	[49]
130	Terpinolene	$C_{10}H_{16}$	[71]
131	Limonene	$C_{10}H_{16}$	[71]
132	Piperitenone oxide	$C_{10}H_{14}O_2$	[72]
133	3-Isopropylphenol	$C_9H_{12}O$	[70]
134	2-Isopropylphenol	$C_9H_{12}O$	[70]
135	4-Isopropylphenol	$C_9H_{12}O$	[70]
136	Varamol-106	$C_9H_{10}O_2$	[73]
137	Naphtalene	$C_{10}H_8$	[71]
138	Geijerene	$C_{12}H_{18}$	[69]

(*Continued*)

Table 4 (Continued).

No.	Compounds	Chemical Formula	References
139	1-Methyl-5,6-divinyl-1-cyclohexene	$C_{11}H_{16}$	[74]
140	4H-pyran-4-one,2,3-dihydro-3,5-dihydrox	$C_6H_{10}O_4$	[49]
141	(z)-8-(3,5-Dimethyl-4-hydroxyphenyl) −2-O	$C_{15}H_{16}O_2$	[49]
142	Acetic acid	$C_{11}H_{22}O_2$	[68]
143	Butyl hydroxyl anisole	$C_{11}H_{16}O_2$	[49]
144	Camphor	$C_{10}H_{16}O$	[75]
145	Borneol	$C_{10}H_{18}O$	[76]
146	Chrysanthenone	$C_{10}H_{14}O$	[76]
147	Elemol	$C_{15}H_{26}O$	[72]
148	Isobornyl acetate	$C_{12}H_{20}O_2$	[76]
149	Cedrol	$C_{15}H_{26}O$	[76]
150	(–)-Loliolide	$C_{11}H_{16}O_3$	[73]
151	Myrcene	$C_{10}H_{16}$	[71]
152	2,7-Dimethyl-3,6-dimthylene-1,7-octadiene	$C_{12}H_{18}$	[74]
153	α-farnesene	$C_{14}H_{22}$	[69]
154	2-Nonanone	$C_9H_{18}O$	[74]
155	2-Decanone	$C_{10}H_{20}O$	[74]
156	2-Undecanone	$C_{11}H_{22}O$	[74]
157	2-Dodecanone	$C_{12}H_{24}O$	[74]
158	2-Tridecanone	$C_{13}H_{26}O$	[74]
159	2-Nonadecanone	$C_{19}H_{38}O$	[49]
160	2-Nonanol	$C_9H_{20}O$	[71]
161	2-Undecanol	$C_{11}H_{24}O$	[71]
162	Octyl acetate	$C_{10}H_{20}O_2$	[71]
163	Nonyl acetate	$C_{11}H_{22}O_2$	[71]
164	2-Docyl acetate	$C_{12}H_{24}O_2$	[71]
165	Dodecyl acetate	$C_{14}H_{28}O_2$	[77]
166	Pentadecanolide acetate	$C_{17}H_{30}O_4$	[78]
167	Decanoic acid	$C_{10}H_{20}O_2$	[49]
168	Dodecanoic acid	$C_{12}H_{24}O_2$	[73]
169	Palmitic acid	$C_{16}H_{32}O_2$	[73]
170	Heptadecanoic acid	$C_{17}H_{34}O_2$	[73]
171	8-Phenyl-2-octanone	$C_{14}H_{20}O$	[69]
172	Diethyl phthalate	$C_{12}H_{14}O_4$	[78]
173	Methyl-3-Hydroxy-3-(4-hydroxy-3,5-dimethoxyphenyl)-propanoate	$C_{12}H_{16}O_6$	[37]
174	Methyl-3-(4-Hydroxy-3,5-dimethoxyphenyl)-oxirane-2-carboxylate	$C_{12}H_{14}O_6$	[37]
175	Hexahydrofarnesyl acetone	$C_{18}H_{36}O$	[73]
176	Nonan-2-yl 2-methylbutanoate	$C_{14}H_{28}O_2$	[73]
177	Phytol	$C_{20}H_{40}O$	[73]
178	2-Undecanol, propyl ester	$C_{14}H_{28}O_2$	[74]
179	2-Undecanol,2-methyl propyl ester	$C_{15}H_{30}O_2$	[74]
180	2-Undecanol,2-methyl butyl ester	$C_{16}H_{32}O_2$	[74]
181	Methyl laurate	$C_{13}H_{26}O_2$	[49]
182	Methyl hexadecanoate	$C_{17}H_{34}O_2$	[73]
183	2-Methyl-undecanal	$C_{12}H_{24}O$	[72]
184	2-Heptanol acetate	$C_{10}H_{20}O_2$	[72]
185	Nonyl cyclopropanecarboxylate	$C_{13}H_{24}O_2$	[74]
186	Methyl oleate	$C_{19}H_{36}O_2$	[73]
187	Linoleic acid	$C_{18}H_{32}O_2$	[73]

(*Continued*)

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Table 4 (Continued).

No.	Compounds	Chemical Formula	References
188	2-Methyl-7-octadecyne	$C_{19}H_{36}$	[49]
189	Docosene	$C_{22}H_{44}$	[49]
190	2-Octyl acetate	$C_{10}H_{20}O_2$	[71]
191	2-Nonyl acetate	$C_{11}H_{22}O_2$	[71]
192	2-Undecanol, 2-acetate	$C_{13}H_{26}O_2$	[69]
193	2-Acetoxy tetradecane	$C_{16}H_{32}O_2$	[68]
194	Hexadecanol	$C_{16}H_{34}O$	[49]
195	4-Butoxy −2-hydroxybenzonitrile	$C_{11}H_{13}NO_2$	[49]
196	4-Methoxy-benzoic acid cyclopentylidene-hydrazide	$C_{13}H_{16}N_2O_2$	[49]
197	1-(1,3-Benzodioxol-5-ylmethyl)-3-Nitro-1	$C_7H_6O_2$	[49]
198	Safrole	$C_{10}H_{10}O_2$	[30]
199	1,5-Isobutyl-1,3-benzodioxole	$C_{11}H_{14}O_2$	[74]
200	Ethyl piperonyl acetate	$C_{12}H_{14}O_4$	[74]
201	6-(1,3-Benzodioxol-5-yl)-hexan-2-yl acetate	$C_{15}H_{20}O_4$	[69]
202	8-(1,3-Benzodioxol-5-yl)-octan-2-ol	$C_{15}H_{22}O_3$	[69]
203	4-(1, 3-Benzodioxol-5-yl)-butan-2-yl acetate	$C_{13}H_{16}O_4$	[69]
204	8-(1,3-Benzodioxol-5-yl)-octan-2-yl acetate	$C_{17}H_{24}O_4$	[69]
205	1-Methoxy-10*H* -Phenothiazine	$C_{13}H_{11}NOS$	[49]
206	p-Dimethylaminobenzylidene p-anisidine	$C_{16}H_{18}N_2O$	[49]
207	3-Acetamido −4-hydroxy −2(1*H*) -quinolinone	$C_{11}H_{10}N_2O_3$	[49]
208	Chlorpyrifos	$C_9H_{11}Cl_3NO_3PS$	[49]
209	Musk xylene	$C_{12}H_{15}N_3O_6$	[49]
210	7a,9a-Dihydro,1,7a,9a-trimethyl-3*H*-(1,2)-dioxeto(3′,4′:4,5)-furo(3,2-f)-benzopyran-3-one	$C_{14}H_{12}O_5$	[49]
211	2,2 -Dihexylmalonic acid, diethyl ester	$C_{19}H_{36}O_4$	[49]
212	Butyl cyclohexylphthalate	$C_{18}H_{22}O_{42}$-	[49]
213	Octadecane	$C_{18}H_{38}$	[67]
214	Nonadecane	$C_{19}H_{40}$	[67]
215	Eicosane	$C_{20}H_{42}$	[67]
216	Docosane	$C_{22}H_{46}$	[67]
217	Tricosane	$C_{23}H_{48}$	[67]
218	Tetracosane	$C_{24}H_{50}$	[67]
219	Pentacosane	$C_{25}H_{52}$	[67]
220	Hexacosane	$C_{26}H_{54}$	[67]
221	Heptacosane	$C_{27}H_{56}$	[67]
222	Octacosane	$C_{28}H_{58}$	[79]
223	Nonacosane	$C_{29}H_{60}$	[67]
224	Hexatriacontane	$C_{36}H_{74}$	[67]
225	3-Methylphenol	$C_7H_8O_2$	[70]
226	4-Methylphenol	$C_7H_8O_2$	[70]
227	Gallocatechin	$C_{15}H_{14}O_7$	[65]
228	Protocatechuic acid	$C_7H_6O_4$	[47]
229	Syringic acid	$C_9H_{10}O_5$	[47]
230	Vanillic acid	$C_8H_8O_4$	[47]
231	Phthalic acid	$C_8H_6O_4$	[67]

methanol or ethanol extracts are the most frequently reported, followed by aqueous, ethyl acetate, and other organic solvent extracts.[20,28,66,80–89]

Antimicrobial Effects

Generally, *R. graveolens* shows inhibitory activity against Gram-positive bacteria, which is superior to that against Gram-negative bacteria. Most studies have reported the antimicrobial activity of alcohol, ethyl acetate, and petroleum ether

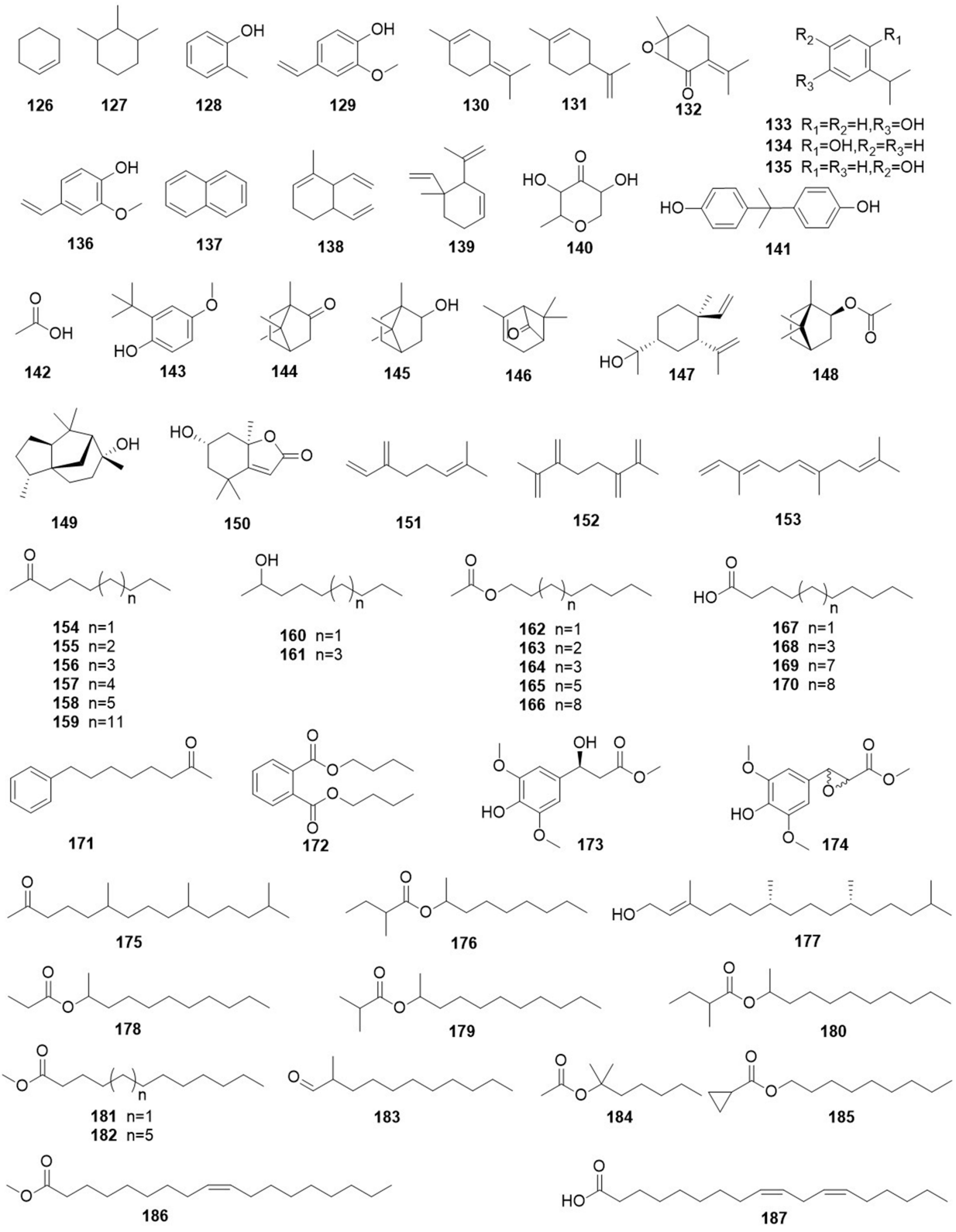

Figure 6 Continued.

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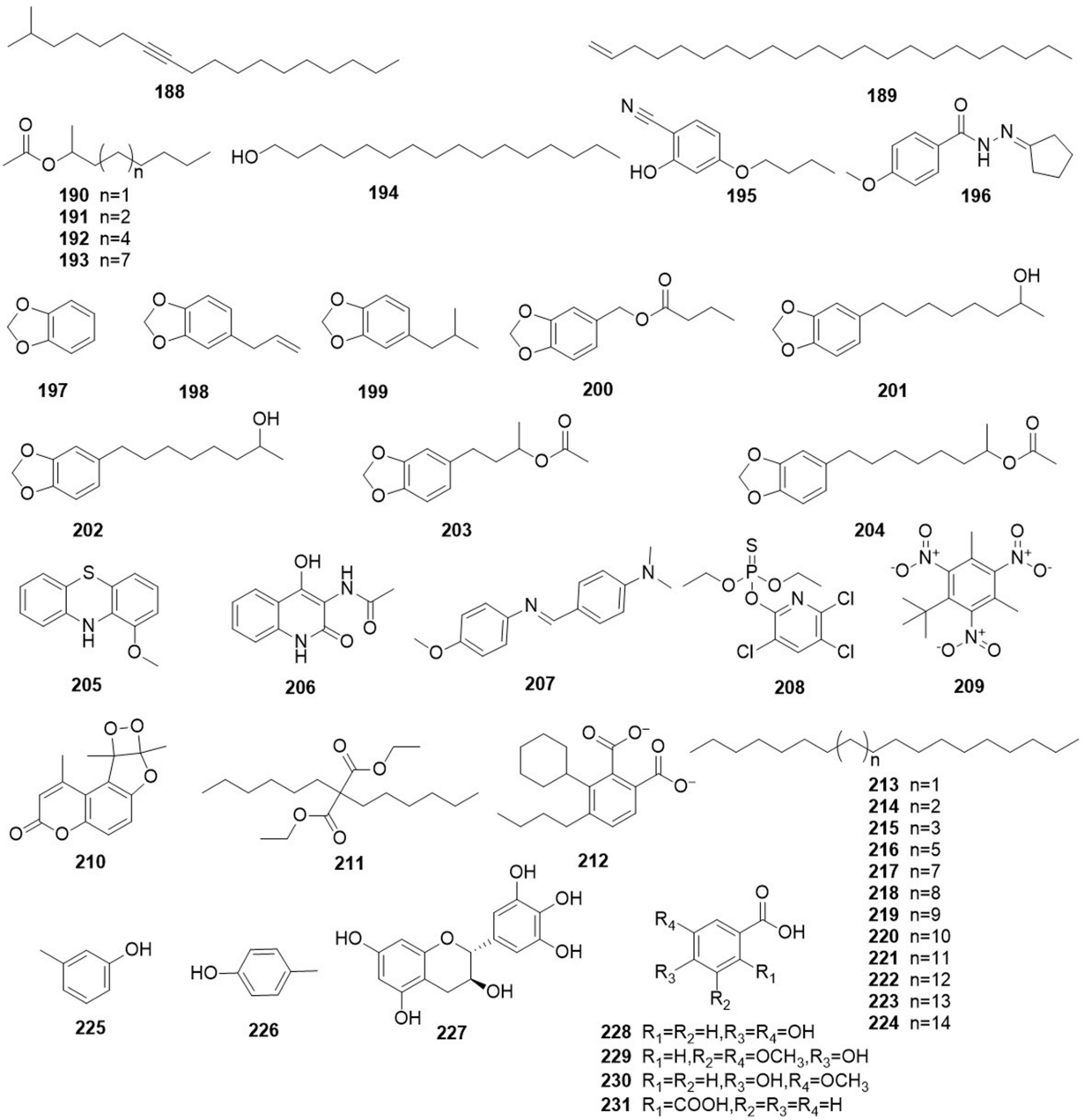

Figure 6 Structures of volatile oil and others in *R. graveolens*..

extracts of *R. graveolens* to be superior to that of aqueous extracts. However, the antimicrobial activity of the volatile oils of *R. graveolens* has been the most widely investigated. Additionally, some compounds including 4, 21, 30, 32, and 62 exhibited antiviral activity.

The 70% ethanol extracts of the leaves and flowers of *R. graveolens* possessed potent anti-*Helicobacter pylori* activity, with a zone of inhibition (ZOI)≥22 mm and MIC ≤5 mg/mL, compared with the positive drugs azithromycin, clarithromycin, metronidazole, and amoxicillin with ZOIs of 30, 25, 14, and 14 mm, respectively. This study also found strong anti-*Helicobacter pylori* activity of coumarin and alkaloid compounds isolated from *R. graveolens* (Minimum inhibitory concentration (MIC) ≤5 mg/mL).[32] The methanol extract of the aerial parts of *R. graveolens* had an inhibitory effect on Gram-negative bacillus *Klebsiella pneumoniae* and, to a lesser extent, typhoid bacillus and *Escherichia coli*. Among Gram-positive bacilli, it exhibited an inhibitory effect on *Staphylococcus aureus*, typhoid bacillus, and *Bacillus*

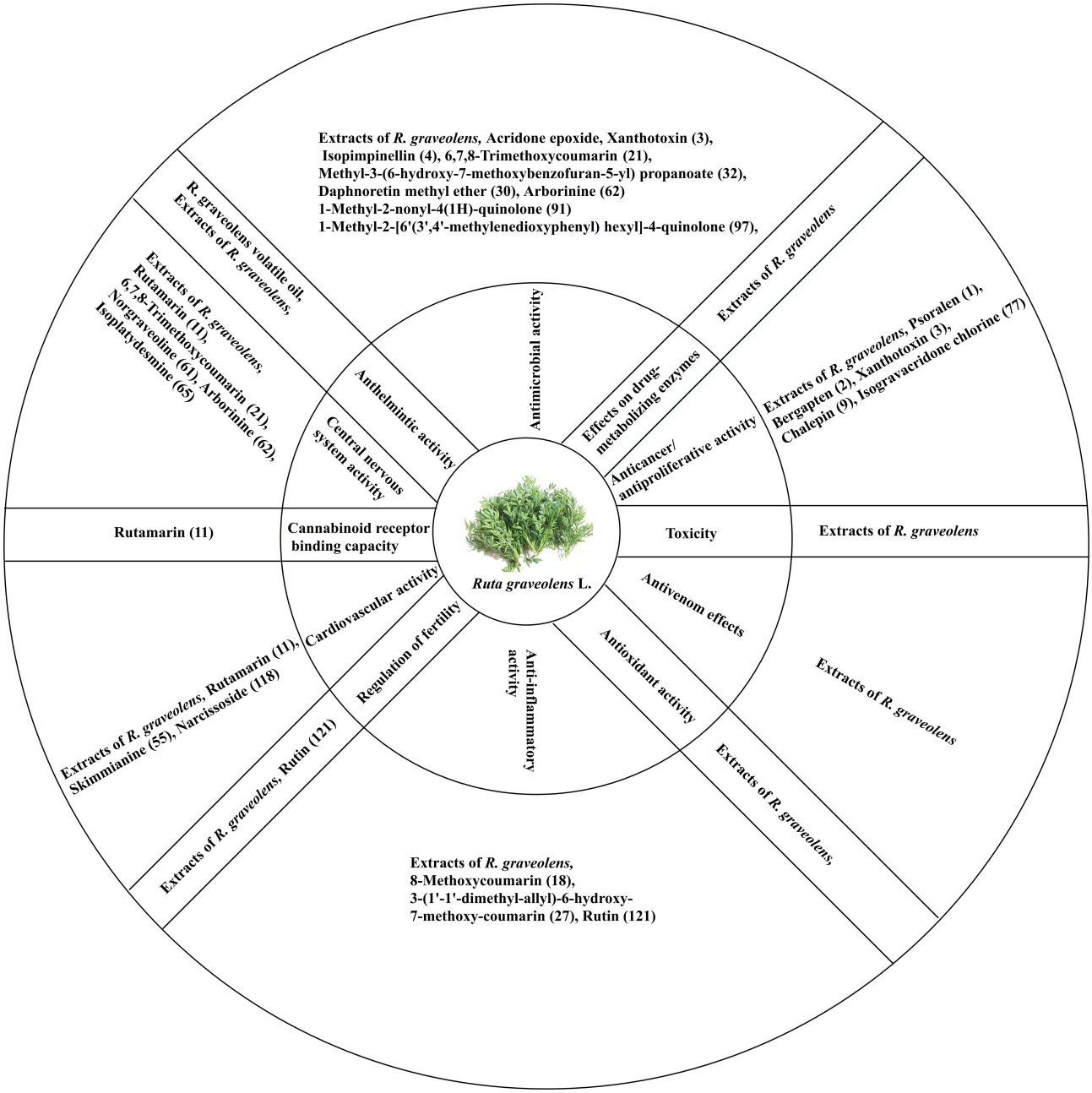

Figure 7 Summary of pharmacological properties of *R. graveolens*..

cereus, compared to the positive controls tetracycline, methicillin, and ampicillin.[90] However, the study only studied the inhibitory effects of a single dosage of methanolic extract and therefore lacked information on dosage effects. The antibacterial activity of aqueous, ethanol, and methanol extracts of *R. graveolens* revealed that methanol (ZOI: 8 mm) and aqueous (ZOI: 4 mm) extracts showed the highest bacteriostatic activity against *P. aeruginosa* and *E. coli*, respectively.[91] This study showed the antimicrobial activity in the extracts of different parts of *R. graveolens* but also lacked a positive control group, compromising the quality of the study. Methanolic, petroleum ether, ethyl acetate, and aqueous methanolic extracts of *R. graveolens* showed bacteriostatic activity and cytotoxicity. All extracts were inactive against the Gram-negative bacteria *E. coli* and *Candida albicans* but showed significant selective inhibitory effects against Gram-positive bacteria, including *S. aureus, Streptococcus pneumoniae, Listeria monocytogenes*, and *B. subtilis*. Only the ethyl acetate extract inhibited the growth of *Corynebacterium diphtheriae* and streptomycin was used as a

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positive control.[20] The antimicrobial activity of different solvent extracts of *R. graveolens* against a variety of bacteria in this study but failed to investigate the dose–activity relationship and lacked a positive control.

The volatile oil of *R. graveolens* leaves exhibits antibacterial activity against Gram-positive and Gram-negative bacteria, with ZOIs ranging from 8.30 to 25.60 mm (MIC = 0.75−1.40 μg/mL). The lowest inhibitory activity was against *P. aeruginosa* and the most susceptible bacteria were *B. cereus* and *S. aureus* ($P < 0.01$) (ZOI: 25.60 ± 0.03 and 22.00 ± 0.06 mm, MIC: 1.0 ± 0.04 and 1.0 ± 0.08 μg/mL, respectively), using as positive controls gentamicin (30 μg/disc) for Gram-positive organisms and amikacin (30 μg/disc) for Gram-negative organisms.[78] This study investigated the MIC of *R. graveolens* volatile oil against various bacteria in positive control groups. The volatile oil of *R. graveolens* was effective (MIC: <0.55 mg/mL) against *S. pneumoniae* strains GC-4, GC-5, GC-6, and GC-11 in a study carried out using piclorin and surfactant as positive controls (MIC: 0.003 and 0.004 mg/mL, respectively).[76]

Acridone epoxide (1 mg/mL, half maximal inhibitory concentration (IC_{50}) 0.125−1.0 μM) from the ethyl acetate extract of *R. graveolens* showed strong antibacterial and antiamoebic activity against the *Colletotrichum* of the plant fungal pathogens *Colletotrichum gloeosporioides* and *Colletotrichum oxysporum*, which was significantly higher than that of commercial fungicides carbendazim and benomyl, at a concentration of 2 μM. Acridone epoxide (0.5 μM) inhibits *B. anthracis* and *B. glabrata* by 100%.[80] In this study, the fungicidal activity of acridone epoxide from *R. graveolens* at six doses and showed its potential to outperform that of the positive control.

In an evaluation of antimicrobial activity of polyphenol extract of *R. graveolens* against five pathogenic strains. *Staphylococcus aureus* was the most sensitive bacteria with an inhibition zone of 14.37 mm and MIC value of 0.625 mg/mL, followed by Listeria monocytogenes (11.75 mm and MIC = 1.25 mg/mL), and Escherichia coli (10.25 mm and MIC = 1.25 mg/mL).[64] However, this study lacked the positive control.

Quinolone alkaloids with antifungal activity in *R. graveolens*, compounds 91 and 97, showed the highest activity at 300 μM against *Acanthamoeba* (50% and 57% inhibition, respectively), which was comparable to the activity of the positive group, benomyl. Compound 97 (100 μM) was the most active against *Anthrax glabrata* (67.7% inhibition) compared to the 66% inhibition of benomyl (300 μM). Compounds 3, 91 and 97 (300 μM) were the most active against *Fusarium acnes* (50%, 37%, and 44% inhibition activity, respectively), although they were less active than the positive groups benomyl and gramicidin (77% and 100% inhibition activity, respectively). The alkaloids were more active than the standard fungicide benomyl (57% inhibition at 300 μM), but their inhibitory activity was the same as that of carbendazim.[36] This study evaluated the antimicrobial activity of coumarins and alkaloids isolated from *R. graveolens* at three concentrations and showed antimicrobial activity superior to that of the positive control against some bacteria. However, these studies did not evaluate the compounds in vivo or investigate their mechanisms of action. The essential oils of *R. graveolens* showed weak inhibitory effects against *Aspergillus flavus* and *Fusarium oxysporum*.[92] Another study showed essential oil of *R. graveolens* has a strong antifungal effect on *C. gloeosporioides* by inducing changes in fungal metabolism and triggered apoptosis-like responses to cell death.[93] Ethyl acetate extract of *R. graveolens* roots yielded rutacridone epoxide with potent selective algicidal activity towards the 2-methyl-isoborneol (MIB)-producing blue-green alga *Oscillatoria perornata*, with relatively little effect on the green alga *Selenastrum capricornutum*.[94] These studies were only conducted in vitro not of in vivo and lacked the MICs investigation.

Compounds 21 and 62 isolated from the aerial parts of *R. graveolens* were potent anti-HRV (human rhinovirus) viral components with IC_{50} values of 11.98 μM and 3.19 μM, respectively. Compounds 4, 30, and 32 were weaker antivirals but displayed significant dose-dependent activity compared to pleconaril as a positive control.[37]

Anti-Inflammatory Effects

In addition to antibacterial activity, polyphenol extract of *R. graveolens* also has anti-inflammatory activity. For the anti-inflammatory activity of polyphenol extract of *R. graveolens*, the highest tested concentration (200 μg/mL) gave 50.61% of inhibition of the denaturation of albumin and 44.12% of membrane stabilization.[64] However, this study was only a simple study of anti-inflammatory activity of polyphenol extract of *R. graveolens* and lacked further exploration such as chemical composition and in vivo testing. The lowest dose of *R. graveolens* (25 mg/kg, i.p.) and pentoxifylline (10 mg/kg, i.p.) produced a significant reduction in pyrexia induced by E. coli (50 μg/kg, i.m.) over the 5-h period of measurement.[95] Again, this study lacked in vivo studies and positive control.

Coumarin 18 obtained from a 50% methanolic extract of *R. graveolens* inhibited inflammatory factors and nuclear factor kappa-B (NF-κB) expression in lipopolysaccharide (LPS)-stimulated mouse J774 macrophages. Nitric oxide (NO) levels were reduced following treatment with compound 18 (5, 10, and 20 μg/mL), which significantly inhibited NO-induced nitrite formation in a dose-dependent manner, and compound 18 (20 μg/mL) significantly inhibited LPS-induced NF-κB (41% inhibition). In an in vivo rat model of rheumatoid arthritis, compound 18 (2 and 20 mg/kg) resulted in a significant reduction in the arthritis index and arthritis score within 15 days, and inhibition of collagen-induced arthritis (CIA) at 42 days was 75% (2 mg/kg) and 84% (20 mg/kg), with inhibition by the higher dose comparable to that of the positive drug indomethacin (87% inhibition). The levels of pro-inflammatory cytokines in rat plasma were also significantly reduced following treatment with compound 18.[38] This study evaluated the anti-inflammatory activity of coumarin analog 18 in high-, medium-, and low-dose groups, showing high efficacy in the treatment of CIA and long-term results comparable to those of the positive control. However, female rats were selected for the study and glucocorticoids in female animals affected the inflammatory response. Further studies should explore anti-inflammatory effects in male rats under the same conditions to exclude the influence of sex. Furthermore, the anti-inflammatory mechanisms should be investigated.

The methanolic extract of *R. graveolens* (median lethal dose (LD_{50}) >4000 mg/kg) at a dose of 100 mg/kg significantly reduced writhing in mice induced by 54% acetic acid, 400 mg/kg significantly delayed the response time to thermal stimuli 15, 30, 45, and 60 min after treatment, and 50−400 mg/kg significantly reduced carrageenan gum-induced oedema. The combination of the lowest dose of *R. graveolens* methanolic extract (25 mg/kg) and indomethacin (10 mg/kg) significantly reduced acetic acid-induced writhing in mice, and the combination of indomethacin (2 mg/kg) significantly reduced carrageenan-induced edema. All combinations were superior to *R. graveolens* methanolic extract of *R. graveolens* and indomethacin alone, whereas paracetamol served as a positive control.[96]

In another study, the anti-inflammatory effects of pre-administration of *R. graveolens* ethanol and methanol extracts (20 and 50 mg/kg) were explored in a mouse model of carrageenan-induced foot edema inflammation using diclofenac (Voveran) as a positive control. Methanolic (20 mg/kg) and ethanolic extracts (50 mg/kg) showed maximum inhibition of foot edema (90.9%), which was superior to the positive control (20 mg/kg, 72.72%). A higher methanolic extract dose (50 mg/kg) resulted in 81.81% inhibition.[87] Although both alcohol extracts exhibited superior anti-inflammatory effects compared to the positive control drug, the inverse dose dependence of the methanol extract should be further explored at lower doses.

A study evaluating the anti-inflammatory activity of *R. graveolens* alkaloid fractions in male rat models of carrageenan-induced acute inflammation and adjuvant-induced chronic inflammation revealed a better anti-inflammatory effect of the alkaloid fraction (10 mg/kg, 83% inhibition of edema) than that of the positive control (70% inhibition of edema). The percentage inhibition of foot volume by *R. graveolens* alkaloids on days 8, 14, and 21 was comparable to that by indomethacin and even superior to that of the positive drug on day 21. Thiobarbituric acid reactants, cyclooxygenase 2.5-lipoxygenase, and myeloperoxidase levels were reduced after *R. graveolens* alkaloid treatment, whereas antioxidant enzyme and glutathione levels were elevated. There was a significant recovery in rats treated with *R. graveolens* alkaloids, and the study was conducted using diclofenac sodium (20 mg/kg, acute) and indomethacin (3 mg/kg, chronic) as positive controls.[82] The results displayed the anti-inflammatory activity of two doses of *R. graveolens* alkaloids against foot swelling, showing stronger effects at lower doses than in the positive control group.

A 50% methanolic extract of *R. graveolens* was screened in vitro using the mouse macrophage cell line J774. The methanolic extract was partitioned using different solvents to examine the anti-inflammatory activity of the ether, chloroform, and ethyl acetate fractions. Only the ether fraction significantly inhibited LPS-stimulated NO levels (70% at 100 μg/mL). Compound 27 in the ether fraction significantly inhibited NO production at doses of 5, 10, and 20 μg/mL (23, 34, and 62%, respectively) compared to the positive drug NO synthesis inhibitor L-NAME (200 μg/mL). In an in vivo mouse model of rheumatoid arthritis (RA), compound 27 (40 mg/kg) significantly inhibited LPS-induced NO synthase and interleukin-1β (IL-1β) production by inhibiting NF-κB activation.[40] However, because there are numerous factors affecting RA, the signaling pathways are extremely complex, and the exact mechanism of action of *R. graveolens* in the treatment of RA requires more in-depth research. A 50% methanol extract of *R. graveolens* (IC_{50} 345 μg/mL) significantly inhibited LPS-induced NO production by mouse macrophage J-774 in a concentration-dependent manner,

with inhibition by 36, 48.3, 51.3, and 68.7% at doses of 200, 300, 400, and 500 μg/mL, respectively ($0.002 \leq P \leq 0.005$), the positive control being L-NAME. Continuing with the isolation of compound 121 from the extract, the inhibitory effect of three concentrations of 121 (20, 40, and 80 μM) on NO production was assessed. At a concentration of 40 μM of compound 121 (comparable to 500 μg/mL of the extract), there was only a marginally significant inhibition of NO production (20%, $P = 0.058$).[86] This study explored the effect of multiple doses of the extract and isolated 121 on NO levels in an inflammatory model; however, the study was only conducted at the in vitro level.

In summary, methanolic extract and alkaloid fractions of *R. graveolens* and some compounds (18, 27, and 121) in *R. graveolens* showed anti-inflammatory effects by significant inhibition of NO synthase and IL-1β production by inhibiting NF-κB activation in collagen-induced arthritis rat or acetic acid-induced writhing in mice or at in vitro level.

Anticancer/Antiproliferative Effects

Aqueous and methanolic extract of *R. graveolens*, compound 77, and some furanocoumarins showed anticancer/antiproliferative effects on a series of cancer cell s including adenocarcinoma cell lines, glioblastoma cell, colon cancer cell, breast cancer cell, prostate cancer cell, Dalton's lymphoma ascites (DLA) cell, and Erlich's ascites carcinoma cell. However, most of these studies have been investigated in vitro.

Furanacridone (77) has shown antiproliferative effects on human papillary adenocarcinoma cell lines, particularly MDA-MB-231 and hTERT-HME1 (IC_{50} 2.27 μM, IC_{50} 5.90 μM), with the positive control cisplatin (IC_{50} 19.13 μM and 2.01 μM). Although the IC_{50} of hTERT-HME1 was greater than that of cisplatin, the selectivity of compound 77 was higher than that of cisplatin. This study evaluated the antiproliferative effect of compound 77 at two doses over two time periods in two human papillary adenocarcinoma cell lines.[54] A methanolic extract of *R. graveolens* also showed anticancer activity against MCF-7 cells in a dose-dependent manner (IC_{50} 160 μg/mL).[90] However, this study only evaluated activity against the MCF7 breast cancer cell line at six dose concentrations, without a positive control group.

Aqueous extracts of *R. graveolens* (1 mg/mL) can induce glioblastoma cell death through the activation of extracellular signal-regulated kinase 1/2 (ERK1/2) and protein kinase B (AKT), resulting in cessation of cellular proliferation and induction of cell death after 24 h of incubation.[82] Although this study was conducted at multiple doses and evaluated four cell types, the antiproliferative effect on glioblastoma was investigated with a single dose of the aqueous extract of *R. graveolens* without a positive drug group for comparative evaluation.

An 80% methanolic extract of *R. graveolens* induced the P53 pathway and DNA damage and inhibited AKT activation. It decreased the viability and clonogenicity of colon cancer HCT116, breast cancer MCF7, and prostate cancer DU-145 and PC3 cells in a dose-dependent manner, with IC_{50} values of 75, 150, 200, and 300 μg/mL, respectively. Colony formation was inhibited by nearly 100% in all cell lines at a dose of 60 μg/mL. In a study of the effect on untransformed cells, extracts higher than 150 μg/mL showed no specific cytotoxicity in fibroblasts.[97] This study revealed the inhibitory effects of the methanolic extracts of *R. graveolens* on a wide range of cancer cell lines. Unfortunately, comparative studies of positive drugs are lacking.

A 75% methanolic extract of *R. graveolens* was found to be cytotoxic (IC_{100} 16 mg/mL) against Dalton's lymphoma ascites (DLA) and Erlich's ascites carcinoma (EAC), prolonging the lifespan of tumor-bearing animals. The extract of *R. graveolens* exhibited hydroxyl radical scavenging and lipid peroxidation inhibiting effects at low concentrations; however, at high concentrations, as a pro-oxidant, the inhibitory effects on lipid peroxidation and hydroxyl radical scavenging were reduced. The in vivo results showed that, for animals with DLA-containing tumors, lifespan increased by 21.6% in the 400 mg/kg extract group, 43.2% in the 200 mg/kg extract group, and 66.5% in the 80 mg/kg extract group ($P < 0.001$). For animals with EAC-containing tumors, lifespan was increased by 45.0% ($P < 0.01$) in the 400 mg/kg extract group, 81.1% ($P < 0.001$) in the 200 mg/kg extract group, and 38.9% ($P < 0.005$) in the 80 mg/kg extract group.[85] This study revealed the effects of high and low doses of *R. graveolens* methanolic extract on the lifespan of two tumor-bearing animals, although a positive control was not used. The roots, leaves, and aerial parts of *R. graveolens* showed antiproliferative effects on HTLV-1-infected T cell lines MT-1 (10–100 μg/mL for all three parts) and MT-2 (1–10, 10–100, and 1–10 μg/mL for roots, leaves, and aerial parts, respectively). Among the constituents, coumarin analog 9 showed the highest activity (median effective concentration (EC_{50}) 2.87 μM and 1.91 μM, respectively).[63]

DNA topoisomerases are cellular enzymes essential for cell proliferation and are important cellular targets for anticancer interventions. The constituents of the methanolic extract of *R. graveolens* with strong topoisomerase I inhibitory activity have been previously reported.[98] Compound 1 at 20 μM showed 100% inhibitory activity against topoisomerase, compound 2 at 10 μM showed complete inhibition of DNA-enzyme complex formation, and compound 3 showed inhibitory activity only at a higher concentration of 40 μM. Compounds 1, 2, and 3 showed dose-dependent activities, with IC_{50} values of 11, 6.5, and 28 μM, respectively. The inhibitory effects of three furanocoumarins on topoisomerases at high, medium, and low doses and set up a positive control (Camptothecin (20 μM)) to reveal the antiproliferative potential of coumarins in this study. Future studies should attempt to identify these underlying mechanisms.

R. graveolens extract showed high cytotoxic activity against two Burkitt's lymphoma cell lines, RAJI and RAMOS, with an IC_{50} equal to 24.3 μg/mL and 35.2 μ/mL, respectively, and LNCap-FGC-10, a prostate adenocarcinoma cell line with an IC_{50} equal to 27.6 μg/mL as well as Mehr-80, a newly established large cell lung carcinoma (IC_{50} = 46.2 μg/mL).[99] The study needs to further investigate in vivo and its mechanism.

Antioxidant Activity

Strong antioxidant activity was exhibited by an 80% ethanolic extract of *R. graveolens* in in vitro experiments, in which 12 doses (9 μg/mL) were required to achieve 50% scavenging of 1.1-diphenyl-2-picrylhydrazyl free radical (DPPH).[90] However, this study only briefly explored the effect of *R. graveolens* on a single indicator of oxidative response, whereas multiple indicators of oxidative stress in the positive control group would provide a stronger validation of antioxidant activity. *R. graveolens* extract displayed antimicrobial property with Fe^{2+} chelating property (IC_{50} = 0.671 ± 0.013 mg/mL) by Fe^{2+} chelating activity assay.[100] The total phenolic content of *R. graveolens* showed antioxidant activity (72.53 ± 0.31%) at 13.3 μg mL^{-1} concentration and the best antibacterial efficiency against all the tested strains, especially gram-negative *P. aeruginosa*.[101] However, the study was limited to in vitro application. *R. graveolens* extract and rutin significantly increased learning and improved spatial memory, as well as secondary latency. Moreover, there were significant increases in the serum and brain antioxidant capacity as well as the level of thiobarbituric acid reactive substances in serum and brain tissues through scavenging DPPH radical.[102] However, its mechanism needs to be deeply investigated. *R. graveolens* extract exhibited a high inhibition on aldehyde oxidase activity (89–96%) at 100 μg/mL which was comparable with 10 μM of menadione.[84] In an in vivo study of Nickel(II) oxide (NiO)-induced cancer model mice, *R. graveolens* stem lectins (1.0 mg/kg) provided useful antioxidant activity but were shown to be pro-oxidant at higher doses (1.5 mg/kg).[103] The authors concluded that, while a lower dose of lectins could regulate oxidative stress in a cancer system, higher doses were unsuitable as antioxidants. In an in vitro antioxidant model, the DPPH radical scavenging activity of the ethanolic extract of *R. graveolens* leaves was concentration-dependent (8.48%, 10.45%, 11.15%, 13.01%, and 19.37% at concentrations of 10, 50, 100, 250, and 400 μg/mL, respectively). The IC_{50} values of the extract and the positive control butylated hydroxyanisole (BHA) were 160.09 and 325.25 μg/mL, and the IC_{50} values for NO radical scavenging were 540.41 and 638.01 μg/mL, respectively, also indicating iron-reducing ability. The extract also inhibited α-amylase in a concentration-dependent manner (70.78, 72.23, and 72.53% at 2, 20, and 200 μg/mL, respectively). Phenolic compounds (13 μg/mL) exerted major antioxidant activity in the ethanolic extract.[83] This study showed a strong concentration-dependent antioxidant capacity with BHA as a control. However, the study was limited to in vitro application. Using a 70% methanolic extract of *R. graveolens*, the inhibitory effect on acetaldehyde oxidase activity was 89–96% at a dose of 100 μg/mL, comparable to 10 μg/mL of methylenedione, a specific inhibitor of acetaldehyde oxidase. The IC_{50} values for inhibition of benzaldehyde, vanillin, and phenothiazine oxidation were 10.4, 10.1, and 43.2 μg/mL, respectively. The inhibition of the enzyme activities of quercetin and rutin, which were isolated from the extract at 10 μM, was 70–96% and 27–52%, respectively.[84] This study set up multiple dose groups to assess the antioxidant activity of ethanolic extracts of *R. graveolens* at the enzyme level, which could provide insights into the potential in vivo antioxidant mechanisms.

An in vivo study showed that *R. graveolens* alkaloids inhibited the oxidative stress response in hypercholesterolemia, and the levels of antioxidant enzymes, such as superoxide dismutase, catalase, glutathione peroxidase, and glutathione in rabbits were significantly increased by 10 mg/kg alkaloid treatment (LD_{50} > 525 mg/kg), whereas the activities of

cyclooxygenase-2 (COX-2), 15-lipoxygenase (15-LOX), and myeloperoxidase (MPO) were significantly inhibited.[25] However, only the normal control group was used in this study, with no positive controls.

In a word, ethanolic and methanolic extracts of *R. graveolens* and *R. graveolens* alkaloids showed significant antioxidant activity. The specific antioxidant compounds in these extracts need to be further explored.

Regulation of Fertility

Alcohol extract of *R. graveolens* that were used traditionally in medieval Persian medicine as male contraceptive drugs.[104] Extracts of *R. graveolens* and some compounds exhibited the strongest uterodilatory activity. Therefore, pregnant women need to pay attention to the use of this traditional medicine and try to avoid it.

The methanolic, ethyl acetate, n-butanol, and aqueous extracts of *R. graveolens* and the main isolated compounds were assayed for uterotropic activity. The n-butanol extract exhibited the strongest uterodilatory activity in a dose-dependent manner, representing 13.76, 48.62, and 67.58% of the response to oxytocin at concentrations of 0.25, 0.375, and 0.5 mg/mL, respectively. Compound 121, isolated from the n-butanol extract, showed a maximal uterodilatory response at 0.25 mg/mL, representing 68.7% of the selected concentration of oxytocin, which was used as a positive control in this study.[51] The coumarin analogs present in the aqueous extract of *R. graveolens* and their high permeability and acidity had an immobilizing effect on sperm motility. Hexane, chloroform, acetone, and ethanol fractions (100 mg/mL) significantly reduced sperm viability after 1 and 2 h, and the aqueous extract (100 mg/mL) immobilized all spermatozoa immediately and was therefore used as a positive control. A significant difference was observed between 10 μM coumarin analog 3 and the control, but coumarins beyond 10 μM could not be completely solubilized in the semen and thus it was not possible to assess the effect of higher concentrations. Since K^+ channels are involved in sperm viability and volume regulation, blockage of K^+ channels impairs both parameters. Considering the blocking effect of coumarin on K + channels, it is more likely that the blockage of sperm K^+ channels leads to reduced sperm viability.[105]

In the in vivo study, rat sperm viability was determined after 0.5, 1, 2, 4, and 6 h of gavage with an aqueous extract of *R. graveolens* (5 g/kg). Sperm viability significantly decreased after 1 h of administration compared to that of the control ($P < 0.01$), and motility increased gradually with time and was the same as that of the control at 6 h. The testosterone levels, sperm morphology, and DNA structure of the treated groups did not show any significant changes compared to those of the control group, and the spermatozoa only showed significant temporary quiescence, suggesting that *R. graveolens* has the potential to be used for male contraception.[80] The aqueous extract of *R. graveolens* inhibited androgenic activity in male albino rats, and 500 mg/kg significantly reduced the weight of reproductive organs compared with the control ($P < 0.01$). Sperm viability and density of the testicular epididymal tail and ducts, spermatogenic activity of the sleeping tubules, and number of spermatocytes and spermatids in the cell population of rat testes were significantly reduced ($P < 0.001$). Testosterone and follicle-stimulating hormone levels in rats were decreased, and sexual behavior was suppressed in adult male rats ($P < 0.001$).[81] However, with only blank distilled water control, there was a lack of a positive control in this study.

Oral administration of *R. graveolens* extract can interfere with preimplantation development and embryo transport.[106] However, there was a lack of mechanism investigation in this study. Another study demonstrated the spermatogenesis reducing properties of the ethanol extracts of R. graveolens in the adult male Wistar rats, but more studies are necessary to reveal the mechanism of action that is involved in spermatogenesis.[104]

Central Nervous System Activity

The aqueous extract of *R. graveolens* inhibited acetylcholinesterase (AChE) (IC_{50} 50 μg/mL) and butyrylcholinesterase (BuChE) activity compared to the galantamine hydrobromide positive control, with 400 μg/mL showing the strongest inhibition.[88] The hexane extract of *R. graveolens* had anti-AChE and BuChE potential (400 μg/mL, 94.9 ± 2.1% and 86.0 ± 1.9% inhibition, IC_{50} 34 and 61 μg/mL, respectively).[107] Compound 62 showed the strongest AChE inhibitory activity (IC_{50} 34.7 ± 7.1 μM) compared to galanthamine positive control (IC_{50} 3.2 ± 1.0 μM), and compounds 65, 61, and 21 showed mild inhibitory activity (205.6 ± 16.3, 197.3 ± 18.0, and 395.8 ± 68.5 μM).[37] Most of the above studies on anticholinergic activity evaluated anticholinergic semi-inhibition using galantamine as a positive control.

Monoamine oxidase (MAO) is a recognized target in various central nervous system (CNS) disorders. MAO is a mitochondrial outer membrane-bound mammalian flavoprotein enzyme that exists in two isoforms, A and B (MAO-A and MAO-B). Both isoforms are responsible for catecholamine and serotonin catabolism, and have been implicated in a variety of neurological disorders. It has been shown that the dichloromethane extract of *R. graveolens* (9.78 mg/mL) and compound 11 (6.17 μM) isolated from the extract are potent inhibitors of human MAO-B with inhibition rates of 89.98% and 95.26%, respectively. The extract inhibited human MAO-A by 88.22%. Compound 11 decreased the inhibition of hMAO-B to 25.15% but was more selective for hMAO-B.[108] The positive controls for this study were crotagyline (3.67 μM) and selegiline (5.34 μM) with 99.29% and 99.07% inhibition, respectively, and although the crude extract of *R. graveolens* and compound 11 were not as active as the positive drug in terms of anti-MAO activity, the results showed their potential CNS activity.

R. graveolens showed potential central nervous system activity by inhibiting AChE, BuChE, and MAO. Compounds in *R. graveolens* especially coumarins were deserved further evaluation of their role in Parkinson's disease and Alzheimer's disease.

Cardiovascular Activity

Compound 55, 118, and aqueous extracts of *R. graveolens* showed cardioprotective activity in intervene angiogenesis or impair the formation of vascular networks.

Compound 55, a major constituent of *R. graveolens*, selectively inhibited 5-hydroxytryptamine-induced vascular responses in rats, and similar inhibitory effects were observed in isolated atrial samples. In addition, at higher concentrations, compound 55 produced a non-specific blockade of cardiovascular function.[109] The aqueous extract of *R. graveolens* exhibited positive frequency and positive inotropic effects on isolated right atria, which were also studied and explored in six dose scenarios, all of which gave results that were significantly different from those of the blank group. The co-administration of *R. graveolens* with other plant extracts was also tested to investigate the interaction. However, the study only examined the effect of *R. graveolens* aqueous extract on the cardiovascular system at the tissue and organ levels in vitro and there was no positive control.[110]

It was also reported that aqueous extracts of *R. graveolens* were able to dose-dependently disrupt the formation of cellular networks without affecting cell viability, and vascular endothelial factor (VEGF) gene expression was reduced by 20% and 35% compared to the control when stimulated with 0.1 and 1 mg/mL of the extracts, respectively. This suggests that aqueous extracts of *R. graveolens* are a potential therapeutic tool for the intervention of pathological angiogenesis. Compound 118 was also investigated and found to significantly impair the formation of vascular networks, without affecting cell viability. The target sites of action for angiogenesis were explored. Unfortunately, this study used only a blank control and failed to explore the comparative effects of a positive drug.[66]

Other Effects

In addition to the aforementioned activities, *R. graveolens* also exhibits other activities, such as anthelmintic activity, effects on drug-metabolizing enzymes, cannabinoid receptor binding capacity, and antivenom effects.

Anthelmintic Activity

A fumigant and contact toxicity bioassay were used to evaluate the anti-insect activity of the essential oil of *R. graveolens* flower and leaf extracts against maize weevils, rice weevils, and tobacco beetles, using dichlorvos as a positive control. The LD_{50} value of *R. graveolens* volatile oil fumigant was 0.480 and 0.527 mg/cm^3 against corn weevil and rice weevil, respectively, and 0.592 and 0.618 mg/cm^2 by contact toxicity bioassay.[70] The insecticidal activity of ethanolic extracts of *R. graveolens* was also found to be dose-dependent and significantly different to the control, with LD_{50} and LD_{90} concentrations of 36.4 μL and 60.1 μL, respectively.[73] However, there was no positive control in this study and only a blank control was available.

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Effects on Drug-Metabolizing Enzymes

Aqueous extracts of *R. graveolens* can play a partial role in the induction of cytochrome P450 enzymes (CYP450), with rutin increasing CYP1A activity and furanocoumarin increasing CYP2B activity in the mouse liver. The 7-ethoxyresorcinol O deethylase (EROD) activity significantly increased by 17, 23, and 27% with 0.5, 1, and 2 g/kg extracts, respectively. *R. graveolens* extract (0.25−2 g/kg) significantly increased 7-ethoxyisophenoxazolone-O-deethylase (PROD) activity by 59−102%. *R. graveolens* extract (0.5 g/kg/d) increased CYP1A activity, while furanocoumarins increased CYP2B activity. Male mice treated with *R. graveolens* extract (0.5 g/kg/d) for seven days displayed increased hepatic EROD (CYP1A), methoxytestosterone-O-deethylase (MROD) (CYP1A), and PROD (CYP2B) activities by 27, 47, and 80%, respectively.[89]

Cannabinoid Receptor Binding Capacity

The affinity of the extract and isolated compound 11 to type 2 cannabinoid receptor (CB2) was investigated. The results showed that the inhibition constant (Ki) value of the dichloromethane extract was 16.8 ± 0.9 μg/mL, and that compound 11 had a selective affinity to the cutaneous cannabinoid receptor 2 (CB2) with a Ki value of 2.64 ± 0.2 μg/mL. Cannabinol was used as a positive control.[37]

Antivenom Effects

A related study evaluated the antivenom effects of *R. graveolens* extract. The lowest dose of snake venom to induce plasma coagulation in less than 60s was 1 μL, and the *R. graveolens* dose administered to neutralize the venom and triple coagulation time was considered the effective dose (ED). *R. graveolens* leaf acetone and ethanol extracts showed inhibitory activity against coagulation produced by snake venom, with ED values of 40 and 30 μL, respectively.[111] Unfortunately, this study did not include a positive drug group.

Toxicity

There are relatively few reports on the toxic side effects of *R. graveolens*. According to the current literature, photosensitive dermatitis caused by *R. graveolens* is common,[20] and *R. graveolens* is often used in the treatment of skin diseases such as eczema; therefore, the administration procedure should consider skin protection and dosage control for optimal efficacy of treatment. Because *R. graveolens* has an abortifacient effect and can cause uterine bleeding and inflammation,[34] women should use *R. graveolens* with caution and avoid the drug if pregnant.[112] Other studies that did not observe acute toxicity caused by *R. graveolens*, and it is speculated that *R. graveolens* drying may reduce the content of volatile oils such as methyl nonyl ketone, which may cause uterine hemorrhage. A case of cardiotoxicity, nephrotoxicity, hepatotoxicity, and coagulopathy caused by *R. graveolens* was previously reported in the literature.[113] Although there have been few studies on the mechanism of organ toxicity caused by *R. graveolens*, this case reminds us that it has the potential to cause toxicity in a variety of organs.

Conclusions, Discussion and Future Perspectives

This review summarizes the progress of research on *R. graveolens* and its extract constituents in terms of traditional applications, phytochemistry, pharmacological activities, and toxicology. The research results and shortcomings of this study are also discussed. Although some progress has been made and a solid foundation has been established, there is still room for further exploration. For example, pharmacological research on *R. graveolens* mainly focused on antimicrobial, anti-inflammatory, anti-tumor, and antioxidant activities, and there is little research on the nervous and cardiovascular systems. Many studies have focused on the activity of ethanol, methanol, and water extracts of *R. graveolens*, and the doses studied were very high, which is of limited significance for clinical development. Further extensive evaluation of the activities of *R. graveolens* single-constituent compounds is required, especially for chiral coumarins and alkaloids. There are limited studies on the toxicology of *R. graveolens*, mainly focusing on photosensitive skin diseases and uterine side effects, and there is little research on its effects on the vital organs of the body. Furthermore, there are insufficient correlational analyses of the conformational relationships of non-volatile components such as phenylpropanoids and alkaloids, which are abundant in *R. graveolens*. Modern medical technology has validated the traditional use of *R.*

graveolens, demonstrating a wide range of pharmacological effects and the material basis for its efficacy in many in vitro and in vivo studies; however, further research is required.

Future Perspectives

1. Chiral coumarin isomers and stereochemical configurations should be elucidated.
2. The structural diversity of acridone and quinoline alkaloids in *R. graveolens* warrants further exploration.
3. The study of the single constituent compounds in the aqueous extracts of *R. graveolens* requires full elucidation and comparison with the chemical compositions of alcohol extracts.
4. Based on the traditional use of *R. graveolens* to treat arthralgia caused by rheumatism and inflamed sores, further studies on its antinociceptive and immunomodulatory effects are warranted.
5. The MAO-selective enzyme activity requires further study, especially that of chiral coumarin constituents.
6. Further in vitro and in vivo animal studies are required for toxicological evaluations prior to future clinical studies.
7. Since the plant has antioxidant activity, it can also be explored for anti-obesity, diabetic, hyperlipidemia etc.

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Disclosure

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