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Research progress on the phytochemistry and bioactivity of Kaempferiae Rhizoma

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[Abstract] Kaempferiae Rhizoma (KR), also known as aromatic ginger or sand ginger, is the rhizome of the aromatic plant, *Kaempferia galanga* L. In traditional Chinese medicine, KR is prescribed for pain relief and promoting digestion. In folk medicine, it has a long history for treatment of hypertension, inflammation, and tumors. The plant is widely cultivated as an industrial crop and used as a spice in southern China. KR has attracted increasing interest in the last few decades because of its diverse composition and biologically active constituents. In this review, the volatile oil, terpenes, diarylheptanoids, phenolic acids, and flavonoids isolated from KR are summarized along with discussions of their biological significance for treatment of inflammation, pain, tumors, oxidative stress, and bacterial infection, and for insecticidal properties.

[Key words] Kaempferiae Rhizoma; *Kaempferia galanga* L.; Phytochemistry; Bioactivity

1 Introduction

Kaempferiae Rhizoma (KR) (commonly known as aromatic ginger) is the dried rhizome of the aromatic plant, *Kaempferia galanga* L., Zingiberaceae. The species is distributed in tropical and subtropical Asia, including Guangdong, Guangxi, Yunnan, and Taiwan provinces in China and in other countries, including India, Myanmar, Thailand, Indonesia, Bangladesh. The plant is a popular condiment in this region, but is rarely encountered in Western countries[1-2]. Common names for the species include "Shannai" and "Shajiang" in China[3], and "Sugandhavachaa" in India[4]. KR is commonly used in traditional Chinese medicine (TCM) as a remedy for abdominal pain, diarrhea and indigestion, by moving "Qi", relieving pain and improving digestion[5]. It has been used extensively in folk medicine for treatment of hypertension, inflammation, and tumors. KR is also used to treat sore throat, swelling, and rheumatism, and for deworming in southeast Asia. The rhizome has a strong aroma and is common in condiments and spices[6]. *K. Galanga* is a food crop of significant economic impact in Guangdong, China. Research on KR and its constituents has increased, and many new reports of composition and bioactivity are available. This review examines phytochemicals, bioactivities and mechanisms of action for KR and its constituents to provide a reference for further

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research and use of the material.

2 Phytochemistry

KR contains a variety of bioactive compounds, mainly volatile oils, terpenes, diarylheptanoids, dipeptides, phenolic acids, fatty acids, flavonoids, sterols, sugars, and trace elements. Chemical structures of primary constituents are provided in Fig. 1-3.

2.1 Volatile oils

Volatile oils are important constituents of KR[7]. Chen Fubei et al.[8] used petroleum ether to extract volatile oil using a Soxhlet extractor. 36 compounds were identified by GC-MS, including ethyl *p*-methoxycinnamate (44.38%), pentadecane (13.20%), ethyl cinnamate (11.33%) and ethyl *cis*-*p*-methoxycinnamate (5.81%). Volatile oil components of KR from Guangdong, Guangxi and Yunnan were analyzed by HS-SPME-GC-MS and 42 compounds were identified[9]. Volatile oil components of Hainan KR also were analyzed by steam distillation combined with GC-MS and 19 compounds were identified[10]. Many studies report that the composition and content of volatile oil in KR vary by region, climate, and experimental conditions, but ethyl *p*-methoxycinnamate, pentadecane, and ethyl cinnamate remain the primary components. Ethyl *p*-methoxycinnamate is the main aromatic constituent[11].

2.2 Terpenoids

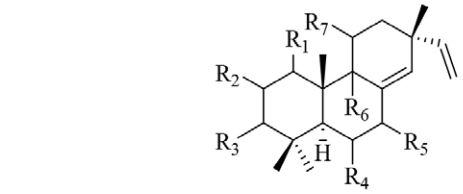
Isopimarane diterpenoids are widely distributed in the Kaempferia[12]. Thirty-five isopimarane diterpenoids (**1-35**) are reported from KR[13-16]. In addition, 4 monoterpenoids (**36-39**) [12,16-17] and 2 sesquiterpenoids (**40-41**)[16] were identified in KR (Table1). The structures of these terpenoids (**1-41**) are provided in Fig. 1.

2.3 Diarylheptanoids

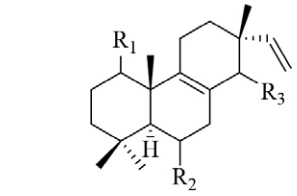
Diarylheptanoids are a class of compounds

Table 1 Terpenoids in Kaempferiae Rhizoma

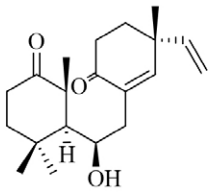
No.	Compounds	Ref
1	Kaempulchraol K	13
2	6*β*-Acetoxysandaracopimaradiene-9*α*-ol-1-one	13
3	6*β*-Acetoxysandaracopimaradiene-1*α*,9*α*-diol	13
4	Kaempulchraol L	14
5	Sandaracopimaradiene-9*α*-ol	14
6	Kaempulchraol I	14-15
7	Kaempulchraol E	14-15
8	Boesenberol J	14-15
9	2*α*-Acetoxysandaracopimaradien-1*α*-ol	14-15
10	1,11-Dihydroxypimara-8(14),15-diene	14-15
11	6*β*-Hydroxypimara-8(14),15-diene-1-one	14-15
12	Sandaracopimaradien-6*β*,9*α*-diol-l-one	14-15
13	1*α*,2*α*,7*β*-Trihydroxypimara-8(14),15-diene	15
14	Sandaracopimaradien-1*α*,2*α*-diol	15
15	Boesenberol J	15
16	1*α*,2*α*-Dihydroxypimara-8(14),-15-dien-7-one	15
17	7*α*-Hydroxyisopimara-8(14),15-diene	15
18	Kaempulchraol F	15
19	Sandaracopimaradien-9*α*-ol-1-one	15
20	(2*R*)-Ent-2-hydroxyisopimara-8(14),15-diene	15
21	Kaempulchraol Q	15
22	(−)-Sandaracopimaradiene	13-15
23	Boesenberol I	13-15
24	Sandaracopimaradiene-1*α*,9*α*-diol	13-15
25	1*α*-Hydroxy-14*α*-methoxyisopimara-8(9),15-diene	13
26	1*α*,14*α*-Dihydroxyisopimara-8(9),15-diene	13
27	Kaempulchraol C	13
28	Kaempulchraol D	13
29	6*β*-Acetoxy-1*α*-14*α*-dihydroxyisopimara-8(9),15-diene	16
30	Kaemgalangol B	15
31	Kaemgalangol C	15
32	Kaemgalangol D	15
33	Kaempulchraol N	15
34	Kaempulchraol O	15
35	Kaemgalangol A	14-15
36	3-Caren-5-one	17
37	(3*R*,4*R*,6*S*)-3,6-Dihydroxy-1-menthene	16
38	(1*R*,2*S*,4*R*)-*p*-Menth-5-ene-1,2,8-triol	16
39	Isoborneol	15
40	Hedytriol	16
41	Oxyphyllenodiol B	16



	R_1	R_2	R_3	R_4	R_5	R_6	R_7
1	H	H	H	β-OAc	H	α-OH	H
2	=O	H	H	β-OAc	H	α-OH	H
3	α-OH	H	H	β-OAc	H	α-OH	H
4	H	H	H	β-OH	H	α-OCH_3	H
5	H	H	H	H	H	α-OH	H
6	α-OH	H	H	H	H	H	H
7	α-OH	H	H	β-OH	H	H	H
8	H	H	H	β-OH	H	H	H
9	α-OH	α-OAc	H	H	H	H	H
10	α-OH	H	H	H	H	H	α-OH
11	=O	H	H	β-OH	H	H	H
12	=O	H	H	β-OH	H	α-OH	H
13	α-OH	α-OH	H	H	β-OH	H	H
14	α-OH	α-OH	H	H	H	H	H
15	H	H	H	β-OH	H	α-OH	H
16	α-OH	α-OH	H	H	=O	H	H
17	H	H	H	H	α-OH	H	H
18	α-OH	H	α-OH	H	H	H	H
19	=O	H	H	H	H	α-OH	H
20	H	β-OH	H	H	H	H	H
21	α-OAc	H	H	β-OH	H	H	H
22	H	H	H	H	H	H	H
23	H	H	H	H	α-OH	α-OH	H
24	α-OH	H	H	H	H	α-OH	H



	R_1	R_2	R_3
25	α-OH	H	α-OCH_3
26	α-OH	H	α-OH
27	H	β-OH	α-OH
28	H	β-OH	β-OH
29	α-OH	β-OAc	α-OH
30	α-OH	β-OH	β-OH
31	α-OH	β-OH	α-OCH_3
32	α-OH	β-OH	α-OCH_2CH_3
33	α-OH	β-OH	α-OH
34	α-OH	β-OH	β-OCH_3



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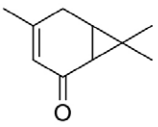

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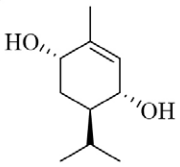

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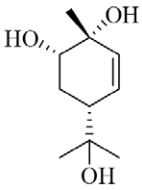

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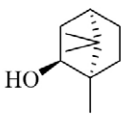

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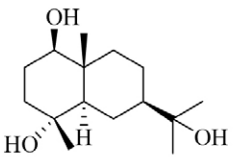

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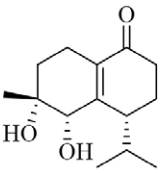

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Fig. 1 Structures of terpenoids in Kaempferiae Rhizoma

built on a 1,7-diarylheptanoid skeleton. These chemicals occur widely in the Zingiberaceae and exhibit antiinflammatory and antioxidant among other activities[18]. The He Xiangjiu research group identified many diarylheptanoids in KR[16,19]. Eight diarylheptanoids from KR were recently isolated and identified (Table 2). Structures (**42-49**) are provided in Fig. 2. Kaempsulfonic acid A (**48**) and kaempsulfonic acid B (**49**) are a pair of sulfonated diphenylheptane isomers[20].

2.4 Dipeptides

Dipeptides isolated from KR were mainly cyclic. Seventeen compounds were identified (**50-66**)[16]. Two pyroglutamic acid derivatives (**67-68**) were also obtained[16] (Table 3).

2.5 Phenolic acids

Phenolic acids are the primary bioactive components of KR. Twenty-one phenolic acids (**69-**

89) have been isolate including 10 cinnamic acids (**69-78**)[15-16, 21] (Table 4). The structures of phenolic acids (**69-77**) are provided in Fig. 3.

2.6 Other compounds

KR also contains abundant fatty acids (**90-100**)[16, 21], flavonoids (**101-103**)[21-23], furan derivatives (**104**), and sterols (**105-106**)[16]. Sugars include fucose, arabinose, xylose, galactose, glucose, rhamnose, mannose, glucuronic acid, and galacturonic acid[24]. In addition, KR contains a variety of trace elements, including relatively high concentrations of K, P, and Mg and lower quantities of Fe, Mn, Zn, Co, Ni[25-26]. Kaempferol (**101**) and kaempferide (**103**) are active components of KR. Related studies have

Table 2 Diarylheptanoids in Kaempferiae Rhizoma

No.	Compounds	Ref
42	(1*R*,3*R*,5*R*)-1,5-Epoxy-3-hydroxy-1-(3,4-dihydroxyphenyl)-7-(3,4-dihydroxyphenyl)-heptane	16,19
43	(1*R*,3*R*,5*R*)-1,5-Epoxy-3-hydroxy-1-(3,4-dihydroxyphenyl)-7-(4-hydroxyphenyl)-heptane 3-*O*-*β*-*D*-glucopyranoside	16,19
44	1-(4-Hydroxy-3-methoxyphenyl)-7-(4-hydroxyphenyl)-heptane-1,2,3,5,6-pentaol	16,19
45	Phaeoheptanoxide	16,19
46	(3*R*,5*S*)-3,5-Dihydroxy-1,7-*bis*(3,4-dihydroxyphenyl)-heptane	16,19
47	Hedycoropyran B	16,19
48	Kaempsulfonic acid A	20
49	Kaempsulfonic acid B	20

Table 3 Dipeptides in Kaempferiae Rhizoma

No.	Compounds	Ref
50	Cyclo-(*L*-VaL-*L*-Phe)	16
51	Cyclo-(*L*-Leu-*L*-I1e)	16
52	Cyclo-(*L*-VaL-*L*-Leu)	16
53	Cyclo-(*L*-VaL-*L*-Val)	16
54	Cyclo-(*L*-Ala-*L*-I1e)	16
55	Cyclo-(*L*-Ala-*L*-Leu)	16
56	Cyclo-(*L*-Ala-*L*-Phe)	16
57	Cyclo-(*L*-VaL-*L*-Ala)	16
58	Cyclo-(*L*-Phe-*L*-Tyr)	16
59	Cyclo-(*L*-Leu-*L*-Tyr)	16
60	Cyclo-(*L*-VaL-*L*-Tyr)	16
61	Cyclo-(*L*-Asp-OCH_3-*L*-Phe)	16
62	Cyclo-(*L*-Tyr-*L*-I1e)	16
63	Cyclo-(*L*-Pro-*L*-Tyr)	16
64	Cyclo-(*L*-Leu-*L*-Phe)	16
65	Cyclo-(*L*-Glu-OCH_3-*L*-Phe)	16
66	*L*-pGlu-*L*-Leu-OCH_3	16
67	Pyroglutamyl-phenylalanine methyl ester	16
68	Pyroglutamyl-tyrosine methyl ester	16

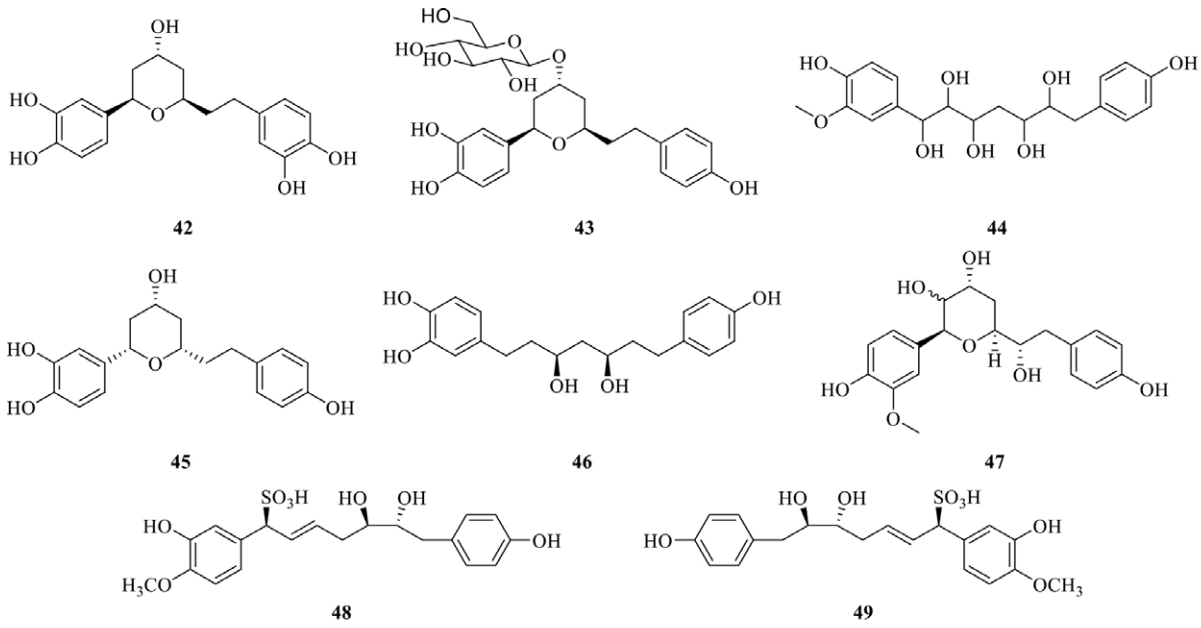

Fig. 2 Structures of diarylheptanoids in Kaempferiae Rhizoma

Table 4 Phenolic acids in Kaempferiae Rhizoma

No.	Compounds	Ref
69	*Trans*-ethyl-*p*-methoxycinnamate	16,21-22
70	Ferulic acid	16
71	*Trans*-*p*-hydroxycinnamic acid	16
72	*Trans*-*p*-methoxycinnamic acid	13,21
73	Ethyl cinnamate	21
74	Ethyl-*p*-methoxycinnamate	15
75	4-Hydroxy-3-methoxyethylcinnamate	15
76	Ethyl-*p*-methoxyhydrocinnamate	15
77	*Cis*-ethyl-*p*-methoxycinnamate	21
78	4-Methoxybenzyl (*E*)-3-(4-methoxyphenyl) acrylate	21
79	Methyl 2,3-dihydroxy-3-(4-methoxyphenyl) propanoate	16
80	Ethyl 2,3-dihydroxy-3-(4-methoxyphenyl) propanoate	15-16
81	Ethyl-*p*-methoxyhydrocinnamate	15
82	1-*O*-4-Carboxylphenyl-(6-*O*-4-hydroxybenzoyl)-*β*-*D*-glucopyranoside	16
83	*p*-Hydroxybenzoic acid	16,21
84	Anisic	16,21
85	Vanillic acid	21
86	Methyl 3,4-dihydroxybenzoate	21
87	4-Methoxybenzyl-*O*-*β*-*D*-glucopyranoside	21
88	Benzoic acid	21
89	Phenylmethanol	21

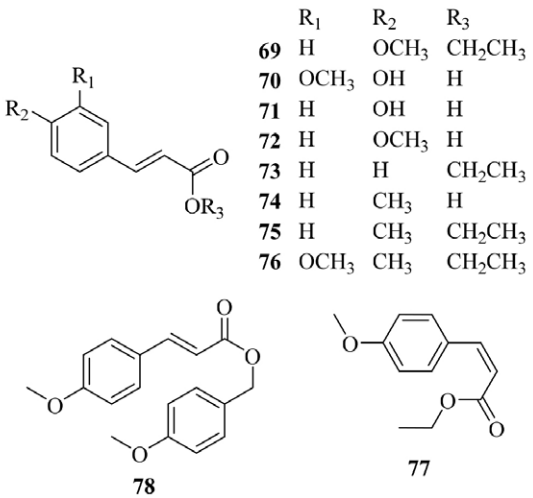

Fig. 3 Structure of representative phenolic acid in Kaempferiae Rhizoma

identified various pharmacological activities, such as antiinflammatory, antitumor and antioxidant[27-29] (Table 5).

Table 5 Other compounds in Kaempferiae Rhizoma

No.	Compounds	Ref
90	Linolenic acid	15
91	Linoleic acid	15
92	Stearic acid	20
93	Dec-5-enoic acid	20
94	Ethyl arachidate	20
95	2-Tetradecenoic acid	20
96	Monopalmitin	20
97	5,6-Dimethyl citrate	15,20
98	3-Carboxyethyl-3-hydroxyglutaric acid 1,5-dimethyl ester	15
99	Trimethyl citrate	15
100	Dimethyl citrate	15
101	Kaempferol	20
102	Luteolin	20
103	Kaempferide	22
104	Furan-2-carboxylic acid	15
105	*β*-Sitosterol	15
106	*β*-Daucosterol	15

3 Bioactivity

KR is commonly used in TCM as a remedy for abdominal pain, diarrhea, and indigestion. Effects are attributed to moving "Qi" (vital energy), relieving pain and promoting digestion. Modern pharmacological studies have found that KR has a variety of pharmacological activities, including antiinflammatory, analgesic, antitumor, antibacterial, antioxidation, and insecticidal, etc.

3.1 Antiinflammation

Various constituents of KR have antiinflammatory properties. This activity is primarily due to inhibiting the production of prostaglandin (PGH_2), tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), nitric oxide (NO) and other inflammatory mediators[19, 30-31].

A chloroform extract of KR is the most active and additional isolation identified the main active ingredient as ethyl *p*-methoxy cinnamate (**69**). *In vitro* experiments demonstrated inhibition of COX-1 and COX-2 as non-selective targets[32]. Other studies, using production of NO in mouse macrophages RAW264.7 induced by lipopolysaccharide (LPS), confirmed the antiinflammatory activity of diterpenoids and diarylheptanoids from KR. Diterpenoids **2**, **3**, **26**, **27**[13] and diarylheptanoids **42**, **43**, **44**, **45**, **46**[19] show good antiinflammatory properties.

3.2 Analgesic effects

Extracts from KR display analgesic activity. Twisting and hot plate methods were used to evaluate analgesic effects of various extracts[33]. Extracts of KR showed obvious analgesic activity. A trichloromethane extract displayed the greatest effects in writhing assays and a petroleum ether extract showed the best analgesic effect on the hot plate. An alcohol extract also exhibited analgesic activity in both hot plate experiments and tail suspension assays with rats[34]. The analgesic effect of KR was enhanced after stir-frying with vinegar[35].

3.3 Antitumor effects

KR extracts show substantial antitumor effects. MTT assays, western blotting, immunofluorescence, and other methods were used, to investigate KR effects on cervical cancer C33A cells[36], cholangiocarcinoma CL-6[37] and HuCCT1 cells[31], oral cancer HSC-3 and Ca922 cells[38], ascites cancer EAC cells[39], gastric cancer SFC-7901 cells[40], human breast cancer MDA-MB-231 cells, and liver cancer WRL-68 cells[25]. KR could inhibit the proliferation and spread of tumor cells and induce apoptosis.

Srivastava et al.[25] reported inhibitory effects of methanol and water extracts and compound **69** on proliferation of 9 cancer cell lines. Notably, strong inhibitory effects were observed on the proliferation of MDA-MB-231 and WRL-68 cells. Kaempferol (**101**) can induce mitochondrial pathway apoptosis by promoting the generation of reactive oxygen species in cancer cells[41]. The volatile oil of KR can inhibit the proliferation and spread of gastric cancer cells *in vitro* and induce apoptosis of gastric cancer cells[40]. In addition, KR polysaccharides effectively protect the thymus and spleen of mice with tumors and improve the immune regulation ability of lymphocytes, and thus inhibit tumor cell proliferation[24].

3.4 Antibacterial effects

KR displays broad-spectrum antibacterial activity against strains, such as *Staphylococcus aureus*, *Bacillus cereus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Candida albicans*, and *Shigella castellani*. Different KR extracts have moderate inhibitory activity toward Gram-positive and Gram-negative bacteria, except *Klebsiella pneumoniae*[33]. Compound **69** inhibited growth of *S. aureus*, *B. cereus*, *E. coli*, *P. aeruginosa* and *C. albicans*, but had no bactericidal activity[42]. Compound **101** downregulates adhesion-related genes of *S. aureus* at the transcription level, reduces the expression of adhesion-related proteins, and decreases the activity of SrtA. These actions reduce the anchoring of adhesion-related proteins, thus inhibiting the formation of *S. aureus* biofilms[43]. The inhibitory effect of an ethanol extract of KR has been used for food preservation[44].

3.5 Antioxidant effects

KR displays significant antioxidant activity, and a methanol extract shows good concentration-dependent scavenging of DPPH free radicals, ABTS free radicals, and NO[39]. Similar activities are reported for scavenging of DPPH ABTS free radicals and hydrogen peroxide[45-47]. A chloroform extract displays the greatest scavenging of DPPH and ABTS free radicals[48].

3.6 Insecticidal activity

KR exhibits insecticidal/nematocidal activity against some mosquito and nematode species. Compound **69** is larvicidal for *Aedes vittatus* and *Anopheles maculatus*[49]. A cyclohexane extract of KR exhibited significant killing of various nematodes. Effective components were compounds **69** and **73** identified through separation and purification. Compound **69** showed the strongest activity[50]. In addition, the volatile oil of KR also had strong nematocidal activity[51].

3.7 Other effects

KR can also be used to make skin whitening agents[52] and sunscreens[53]. Compound **69** also demonstrates vasodilator effects[54]. The ethanol extract of KR may significantly prolong bleeding time in *in vivo* thrombosis animal model experiments[55]. An acetone extract of KR has inhibitory effect on the central nervous system, which can significantly reduce sleep time of mice administered thiopental sodium[56]. An ethanol extract of KR added within 24 hours of pseudorabies virus infection *in vitro* shows significant antivirus activity with an IC_{50} of 55.85 μg/mL[57]. In addition, KR has other biological activities, such as antiangiogenesis[58].

4 Conclusion and Prospect

Understanding of the composition and biological activity of KR has increased year by year, providing new perspectives for individual constituents and clinical applications of KR. In recent years, many reports on flavonoids in KR, especially kaempferol have been published. Kaempferol is the main active compound in KR, displaying powerful antiinflammatory and antitumor activity. In addition, volatile oil and ethyl *p*-methoxycinnamate are also effective components demonstrating antiinflammatory and antibacterial activity. Terpenoids and diarylheptanoids in KR have unique chemical structures and pharmacological activities. These constituents require further study to complete the assessment of the biological activity of KR.

In-depth research continuously increased understanding of KR, but issues still exist. First, KR shows a variety of pharmacological activities but related research was not in-depth. Pharmacological activities of KR and its extracts and specific mechanisms need to be further elucidated. Second, KR, as a dual-use crop with high economic value, is widely planted in many provinces in China, but quality standards have not been established. The content of active components in KR varies in different regions. To control the quality of KR and avoid confusion, adulteration, and counterfeiting, a Chinese medicine fingerprint and characteristic chromatogram of KR should be established as soon as possible. Finally, KR has various biological activities, but its clinical application is limited. It is often used as a spice and adjuvant in foods. As a TCM, KR is usually compatible with drugs in the form of a compound prescription. Experimental information proves that KR is harmless to humans, and its antioxidant, antibacterial and insecticidal/nematocidal activities can be used to develop new natural antioxidants, preservatives, and insecticides.

To promote the utilization of resources, systematic study of chemical constituents of KR, including identification of secondary metabolites, is needed to fully characterize the medicinal value of KR, and enrich the application of KR in food, medicine, cosmetics, and other products.

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