Review Article

Kochiae Fructus, the Fruit of Common Potherb *Kochia scoparia* (L.) Schrad: A Review on Phytochemistry, Pharmacology, Toxicology, Quality Control, and Pharmacokinetics

Wei Zou,[1] **Zhong Tang,**[2] **Yao Long,**[1] **Zuoqi Xiao,**[1] **Bo Ouyang** ⬡,[1] **and Menghua Liu** ⬡[3]

[1]*NHC Key Laboratory of Birth Defects Research, Prevention and Treatment, Hunan Provincial Maternal and Child Health Care Hospital, Changsha 410008, China*
[2]*Breast Disease Department, The First Hospital of Hunan University of Chinese Medicine, Changsha 410007, China*
[3]*Guangdong Provincial Key Laboratory of New Drug Screening, School of Pharmaceutical Sciences, Southern Medical University, Guangzhou 510515, China*

Correspondence should be addressed to Bo Ouyang; 1050495772@qq.com and Menghua Liu; liumenghua@smu.edu.cn

Kochiae Fructus (KF) is the fruit of an annual potherb *Kochia scoparia* (Linn.) Schrad and has been traditionally used for the treatment of diseases in the skin, eyes, and urinary tract for thousands of years in China. Recent studies have showed its anti-inflammatory, antifungal, antiallergic, and antipruritogenic effects to clarify the mechanisms of these actions. Meanwhile, its other effects, such as anticancer, hypoglycemic, and hepatoprotective effects, also have been reported. The achievement of these therapeutic effects is contributed by its chemical constituents. A total of 153 compounds have been identified in KF, mainly including triterpenoids, flavonoids, carbohydrates, amino acids, organic acids, and essential oils. Momordin Ic is the representative triterpene glycoside compound, which is used as a phytochemical marker for the quality control of Kochiae Fructus. The research on toxicity is insufficient, and only one article reported that the LD_{50} was 7.15 ± 0.03 g/kg for water extract of KF after oral administration in KM mice. In addition, the pharmacokinetic study was carried out on momordin Ic with linear pharmacokinetic characteristics. Above all, this review provides comprehensive information about Kochiae Fructus and may provide the theoretic foundation of its clinical application and further development.

1. Introduction

Kochia scoparia (Linn.) Schrad (shown in Figure 1(a)), also called *Bassia scoparia* (L.) A.J. Scott, is a large annual potherb in the family Chenopodiaceae widely distributed in Europe and Asia and naturalized in Africa, Australia, and North and South America [1]. Kochia Fructus (KF, shown in Figure 1(b)) is the fruit of *Kochia scoparia*, which is a spheroidal pentagram with a diameter of 1 to 3 mm [2]. It was first recorded in "Shennong Ben Cao Jing" as a "top grade" medicinal material. Up to now, KF has been used in traditional Chinese and Japanese medicine more than 2000 years for the treatment of diseases of the skin, eyes, and urinary tract [3]. With the deepening

and development of pharmacology research, it has attracted attention particularly because of its antibacterial, anti-inflammatory, antiallergic, antigastric mucosal damage, hypoglycemic, and immunity enhancing effects [4]. Recently, researchers demonstrated that KF mainly contains terpenoids, flavonoids, essential oils, trace elements, and other ingredients. Although there were many researches on the chemical constituents, pharmacological activities of KF, a systematic and updated review is unavailable. Therefore, the aim of this review is to extensively summarize the phytochemistry, pharmacology, quality control, toxicology, and pharmacokinetics of KF, as well as providing novel insights for clinical uses and further researches.
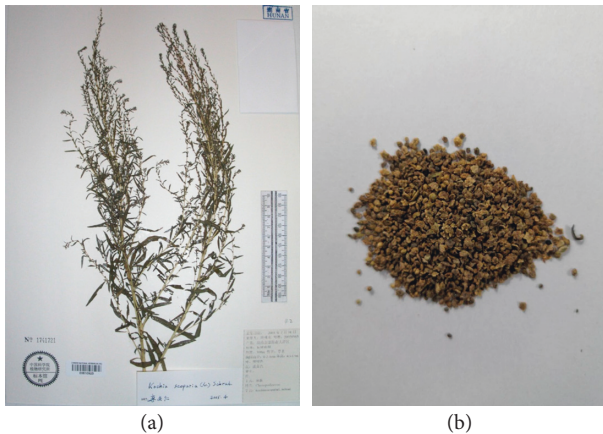
FIGURE 1: (a) The potherb of *Kochia scoparia* (L.) Schrad (http://www.cvh.ac.cn/spms/detail.php?id=f27a89aa) and (b) its fruit Kochiae Fructus.

2. Phytochemistry

With the advancement of analysis technologies such as liquid chromatograph-mass spectrometer (LC-MS), nuclear magnetic resonance-mass spectrometer (NMR-MS), and gas chromatography-mass spectrometer (GC-MS), identification of various components in traditional Chinese medicine has been simplified. To date, 153 compounds within KF, including 25 triterpenoids, 13 flavonoids, 22 carbohydrates (primarily mono- and disaccharides), 21 amino acids, 9 organic acid, 49 essential oils, and 14 heterocyclics, have been identified (Table 1 and Figure 2). Most of investigations indicated that triterpenoids are the main active ingredient within KF. They were characterized with tetracyclic or pentacyclic rings by the polymerization of isoprene. Among them, momordin Ic is a representative triterpenoid saponin with anti-inflammatory effect [5]. Flavonoids were another major component within KF [12]. Most of them are derivatives of flavonol aglycones including quercetin and isorhamnetin. The carbohydrates of flavonoid glycosides are glucopyranose, rhamnose, and galactose. Besides, other flavonoids such as 5,7,4′-trihydroxy-6,3′-dimethoxyflavone and 5,7,4′-dihydroxy-6-methoxyflavone were characterized by LC-MS [6]. KF contains many kinds of amino acid, and current research suggests that certain functional amino acids can play a pharmacological role through the gut-microbiome-immune axis [17]. The essential oil within KF is high fatty acid ester. Yang et al. used a supercritical CO_2 extraction method combined with a gas chromatography-mass spectrometer (GC-MS) method to qualify these essential oil components [14]. Eighteen compounds were isolated and identified, most of which were fatty acid esters and aromatic compounds. The level of the higher fatty acid ester is high, and the relative amount of 9,12-octadecadienoic acid is the highest in oil, followed by 9-octadecenoic acid. Wen et al. used the GC-MS method to qualitatively analyze the essential oil within KF [15]. Compared with the standard mass spectrum, 36 components were identified. Among them, the relative level of high fatty acid esters is the highest, and the amount of terpenoids is small.

3. Pharmacology

Traditionally, according to records of "Shennong Ben Cao Jing," KF was used with the therapeutic effects of diuresis and benefiting pneuma. Compendium of Materia Medica described that the KF could be used in the treatment of red eyes, hemntodiarrhoea, pregnancy combined with gonorrhea, and urinary stoppage [18]. Many other books also depicted the traditional use of KF, which are summarized in Table 2. Modern investigations have proved that KF has anti-inflammatory, hypoglycemic, anticancer, antifungal, antipruritogenic, and antinociceptive effects, as well as antiallergic, antiedema, and hepatoprotective activities. We have enlisted an overview of the pharmacological studies in the following sections (Table 3).

3.1. Anti-Inflammatory Effect. Pharmacological studies showed that anti-inflammatory is a very significant pharmacological activity of KF. In six different animal models (the ddY mice in an acetic acid-induced vascular permeability, the ddY mice in a carrageenin-induced edema, the ddY mice in a compound 48/80-induced edema, the ddY mice in a chemical mediator-induced edema, the ddY mice in an arachidonic acid-induced edema, a picryl chloride-induced ear inflammatory model in ICR mice), the 70% alcohol extract of KF has been proved with obvious inhibition effect on the development of inflammation [19, 20]. The methanol extract of KF was used as a candidate drug for the treatment of inflammatory skin diseases due to its eutherapeutic effect on 1-fluoro-2,4-dinitrofluorobenzene-induced contact dermatitis mice model. The mechanism might be involved in inhibiting the skewing reaction of T helper cell type 1 [22]. The total flavonoids of the KF have shown an anti-inflammatory effect on the dinitrochlorobenzene-induced allergic contact dermatitis rats, and the most likely mechanism of this action involves regulating pERK1/2/TLR4-NF-κB pathway activation [42]. The anti-inflammatory effect of KF was coincident with its traditional use for inflammations in vagina and skin.

Three triterpenoid saponins, namely, 20-hydroxyecdysone, momordin Ic, and oleanolic acid from KF have also been investigated on LPS-stimulated murine macrophage RAW 264.7 cell line. 20-Hydroxyecdysone performed significant inhibitory action on prostaglandin E_2 (PGE_2) generation at the dose of 12.5 μM, while momordin Ic and oleanolic acid showed the anti-inflammatory effect at the dose of 6.25 μM. In addition, momordin Ic significantly reduced productions of tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) at the concentration of 12.5 μM [5].

3.2. Hypoglycemic Effect. KF has shown a potential hypoglycemic effect. Dai et al. illustrated that *n*-butanol fraction of KF could markedly inhibit gastric emptying in normal mice and could more potently inhibit gastric emptying in hyperglycemic and hypoglycemic mice at the dose of 25 mg/kg. The hypoglycemic mechanism is probably related to transportation and transformation of sugar in the digestive

TABLE 1: Chemical compounds identified in Kochiae Fructus.

No.	Compounds	Formula	Ref.
Triterpenoids			
1	20-Hydroxyecdysone	$C_{27}H_{44}O_7$	[5]
2	β-Sitosterol	$C_{29}H_{50}O$	[6]
3	Momordin Ic	$C_{41}H_{64}O_{13}$	[7]
4	Oleanic-acid-3-O-β-D-xylopyranosly(1⟶3)-β-D-glucopyranoside	$C_{41}H_{65}O_{12}$	[7]
5	Momordin I	$C_{41}H_{64}O_{13}$	[7]
6	Oleanolic acid	$C_{30}H_{48}O_3$	[7]
7	Oleanolic acid 3-O-glucuronide	$C_{36}H_{56}O_9$	[7]
8	Oleanolic acid 3-O-β-D-glucopyranoside	$C_{36}H_{56}O_8$	[7]
9	28-O-Deglucosyl-chikusetsusaponin V	$C_{42}H_{66}O_{14}$	[7]
10	$2'$-O-Glucopyranosyl-momordin Ic	$C_{48}H_{76}O_{19}$	[7]
11	Chikusetsusaponin V	$C_{48}H_{76}O_{19}$	[7]
12	Momordin IIc	$C_{47}H_{74}O_{18}$	[7]
13	Kochianoside I	$C_{36}H_{56}O_{10}$	[8]
14	Kochianoside II	$C_{47}H_{74}O_{18}$	[8]
15	Kochianoside III	$C_{41}H_{64}O_{14}$	[8]
16	Kochianoside IV	$C_{41}H_{64}O_{13}$	[8]
17	Daucosterol	$C_{35}H_{60}O_6$	[6]
18	Oleanolic acid 3-O-β-D-xylopyranosyl(1⟶3)-β-D-glucopyranosiduronic acid 6-methyl ester	$C_{42}H_{66}O_{13}$	[6]
19	3-O-β-D-Glucuronopyranosy-28-O-β-D-glucuronopyranosyl-oleanic-acid	$C_{42}H_{66}O_{14}$	[6]
20	Oleanolic acid 3-β-D-glucopyranosiduronic acid 6-methyl ester	$C_{37}H_{58}O_9$	[9]
21	Stigmasterol-3-O-β-D-glucopyranoside	$C_{35}H_{58}O_6$	[8]
22	Oleanic-acid-3-O-[β-D-glucopyranosyl(1⟶2)-β-D-xylopyranosly(1⟶3)]-β-D-glucopyranosiduronic acid	$C_{47}H_{74}O_{18}$	[10]
23	$6'$-Methyl ester of momordin Ic	$C_{42}H_{66}O_{13}$	[11]
24	$2'$-O-β-D-Glucopyranosyl momordin Ic	$C_{47}H_{74}O_{18}$	[11]
25	$2'$-O-β-D-Glucopyranosyl momordin IIc	$C_{53}H_{84}O_{23}$	[11]
Flavonoids			
26	Quercetin 3-O-β-D-apiofuranosyl-(1⟶2)-β-D-galactopyranosyl-7-O-β-D-glucopyranoside	$C_{32}H_{38}O_{21}$	[12]
27	Quercetin 3-O-α-L-rhamnopyranosyl-(1⟶6)-β-D-galactopyranosyl-7-O- β-D-sophoroside	$C_{39}H_{50}O_{26}$	[12]
28	Quercetin 7-O-β-D-glucopyranoside	$C_{21}H_{20}O_{12}$	[12]
29	Quercetin 3-O-β-D-sophoroside	$C_{27}H_{30}O_{17}$	[12]
30	Quercetin 3-O-β-D-galactopyranosyl-7-O-β-D-glucopyranoside	$C_{27}H_{30}O_{17}$	[12]
31	Quercetin 3-O-β-D-apiofuranosyl-(1⟶2)- β-D-galactopyranoside	$C_{26}H_{28}O_{16}$	[12]
32	Isorhamnetin	$C_{16}H_{12}O_7$	[6]
33	Quercetin	$C_{15}H_{10}O_7$	[6]
34	Rutin	$C_{27}H_{30}O_{16}$	[6]
35	Isorhamnetin-3-O-glucoside	$C_{22}H_{22}O_{12}$	[6]
36	5,7,4$'$-Trihydroxy-6,3$'$-dimethoxyflavone	$C_{17}H_{14}O_7$	[6]
37	5,7,4$'$-Dihydroxy-6-methoxyflavone	$C_{16}H_{12}O_6$	[6]
38	Hyperoside	$C_{21}H_{20}O_{12}$	[10]
Carbohydrates			
39	Sorbitol	$C_6H_{14}O_6$	[13]
40	Glucose	$C_6H_{12}O_6$	[13]
41	Galactopyranose	$C_6H_{12}O_6$	[13]
42	Fructose	$C_6H_{12}O_6$	[13]
43	Inositol-scyllo		[13]
44	Trehalose	$C_{12}H_{22}O_{11}$	[13]
45	Sucrose	$C_{12}H_{22}O_{11}$	[13]
46	N-Acetyl glucosamine	$C_8H_{15}NO_6$	[13]
47	Mannitol	$C_6H_{14}O_6$	[13]
48	Mannose	$C_6H_{12}O_6$	[13]
49	Glucosamine	$C_6H_{13}NO_5$	[13]
50	Glycerophosphoric acid	$C_3H_9O_6P$	[13]
51	Rhamnose	$C_6H_{12}O_5$	[13]
52	Ribitol	$C_5H_{12}O_5$	[13]
53	Xylulose	$C_5H_{10}O_5$	[13]
54	Erythritol	$C_4H_{10}O_4$	[13]
55	2-O-Glycerol-α-D-galactopyranoside	$C_9H_{18}O_8$	[13]
56	Maltitol	$C_{12}H_{24}O_{11}$	[13]
57	Melibiose	$C_{12}H_{22}O_{11}$	[13]

TABLE 1: Continued.

No.	Compounds	Formula	Ref.
58	Xylose	$C_5H_{10}O_5$	[13]
59	Ribose	$C_5H_{10}O_5$	[13]
60	Arabinose	$C_5H_{10}O_5$	[13]
Amino acids			
61	Tryptophan	$C_{11}H_{12}N_2O_2$	[13]
62	Tyrosine	$C_9H_{11}NO_3$	[13]
63	Phenylalanine	$C_9H_{11}NO_2$	[13]
64	Methionine	$C_9H_{11}NO_2$	[13]
65	Glutamic acid	$C_5H_9NO_4$	[13]
66	Lysine	$C_6H_{14}N_2O_2$	[13]
67	Glutamine	$C_5H_{10}N_2O_3$	[13]
68	Aspartic acid	$C_4H_7NO_4$	[13]
69	Asparagine	$C_4H_8N_2O_3$	[13]
70	Leucine	$C_6H_{13}NO_2$	[13]
71	Isoleucine	$C_6H_{13}NO_2$	[13]
72	Pyroglutamic acid	$C_5H_7NO_3$	[13]
73	Threonine	$C_4H_9NO_3$	[13]
74	Valine	$C_5H_{11}NO_2$	[13]
75	Proline	$C_5H_9NO_2$	[13]
76	Serine	$C_3H_7NO_3$	[13]
77	Alanine	$C_3H_7NO_2$	[13]
78	Glycine	$C_2H_5NO_2$	[13]
79	Ornithine	$C_5H_{12}N_2O_2$	[13]
80	Cysteine	$C_3H_7NO_2S$	[13]
81	β-Alanine	$C_3H_7NO_2$	[13]
Organic acid			
82	Glucaric acid	$C_6H_{10}O_8$	[13]
83	Gluconic acid	$C_6H_{12}O_7$	[13]
84	Glucuronic acid	$C_6H_{10}O_7$	[13]
85	Citric acid	$C_6H_8O_7$	[13]
86	Gluconic acid-1,5-lactone	$C_6H_{10}O_6$	[13]
87	Threonic acid	$C_4H_8O_5$	[13]
88	Malic acid	$C_4H_6O_5$	[13]
89	Malonic acid	$C_3H_4O_4$	[13]
90	Oxalic acid	$C_2H_2O_4$	[13]
Essential oils			
91	α-Pinene	$C_{10}H_{16}$	[14]
92	2-Camphene	$C_{10}H_{16}$	[14]
93	9-Hexadecenoic acid	$C_{16}H_{30}O_2$	[14]
94	Hexadecenoic acid	$C_{16}H_{30}O_2$	[14]
95	Ethyl hexadecenoic acid	$C_{18}H_{34}O_2$	[14]
96	9,12-Octadecadienoic acid	$C_{18}H_{32}O_2$	[14]
97	Ethyl 9,12-octadecadienoic acid	$C_{20}H_{36}O_2$	[14]
98	9-Ethyl octadecanoate	$C_{20}H_{38}O_2$	[14]
99	Stearic acid	$C_{18}H_{36}O_2$	[14]
100	Methyl hexadecanoate	$C_{17}H_{34}O_2$	[14]
101	Methyl hexadecenoic acid	$C_{17}H_{32}O_2$	[14]
102	Octadeca-9,12,15-trienoic acid	$C_{18}H_{30}O_2$	[14]
103	Methyl 9-octadecenoic acid	$C_{19}H_{36}O_2$	[14]
104	Methyl 10-octadecenoic acid	$C_{19}H_{36}O_2$	[14]
105	Octadecenoic acid	$C_{19}H_{34}O_2$	[14]
106	Methyl 11-eicosenoic acid	$C_{21}H_{40}O_2$	[14]
107	Methyl eicosenoic acid	$C_{21}H_{42}O_2$	[14]
108	Benzene, 1-methyl-2-propyl-	$C_{10}H_{14}$	[15]
109	Cyclohexene, 1-methyl-4-(1-methylethenyl)-	$C_{10}H_{10}$	[15]
110	(E)-3,7-Dimethyl-2,6-octadienal	$C_{10}H_{16}O$	[15]
111	Methyl 2-methyl-octanate	$C_{10}H_{20}O_2$	[15]
112	Benzene, 1-methoxy-4-(1-propenyl)-	$C_{10}H_{12}O$	[15]
113	Methyl nonanoate	$C_{10}H_{20}O$	[15]
114	1-Undecyne	$C_{11}H_{20}$	[15]

TABLE 1: Continued.

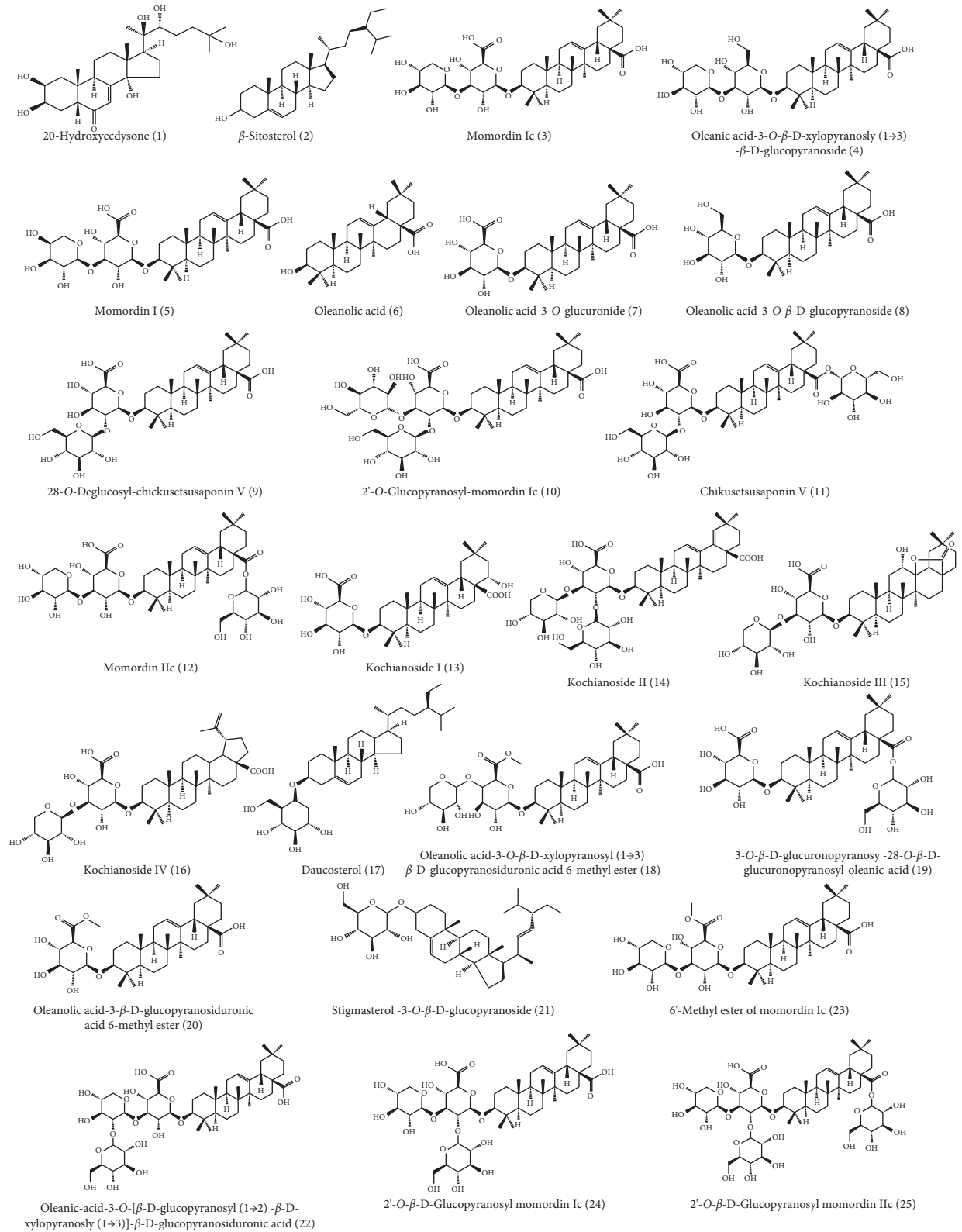| No.	Compounds	Formula	Ref.
115	Ethyl nonanoate	$C_{11}H_{22}O_2$	[15]
116	Naphthalene	$C_{11}H_{10}$	[15]
117	Bicyclo(4,3,1)decan-10-one	$C_{10}H_{16}O$	[15]
118	5-Ethyl-2-nonanol	$C_{11}H_{24}O$	[15]
119	4,8-Dimethyl-1-nonanol	$C_{11}H_{24}O$	[15]
120	(Z)-β-Farnesene	$C_{15}H_{24}$	[15]
121	trans-β-Farnesene	$C_{15}H_{24}$	[15]
122	2,6-Di-T-butyl-1,4-benzoquinone	$C_{14}H_{20}O$	[15]
123	β-Ionone	$C_{13}H_{20}O$	[15]
124	Naphthalene, 1,2,3,5,6,7,8a-octahydro-1,8a-demethyl-7-(1-methyethyl)-[1R-(1α,7β,8aα)]-	$C_{15}H_{24}$	[15]
125	β-Chamigrene	$C_{15}H_{24}$	[15]
126	Ethyl dodecanoate	$C_{14}H_{28}O_2$	[15]
127	Hexadecane	$C_{16}H_{34}$	[15]
128	Methyl tetradecanoate	$C_{15}H_{30}O_2$	[15]
129	Benzene, 1,1'-(1,2-ethynediyl)bis-	$C_{14}H_{10}$	[15]
130	Octadecane	$C_{18}H_{38}$	[15]
131	2-Pentadecanone, 6,10,14-trimethyl-	$C_{18}H_{36}O$	[15]
132	Ethyl pentadecanoate	$C_{17}H_{34}O_2$	[15]
133	Ethyl hexadecanoate	$C_{18}H_{36}O_2$	[15]
134	Eicosane	$C_{20}H_{42}$	[15]
135	Methyl octadecadienoate	$C_{19}H_{34}O_2$	[15]
136	Heneicosane	$C_{21}H_{44}$	[15]
137	Ethyl-octadecadienoate	$C_{20}H_{36}O_2$	[15]
138	Ethyl octadecanoate	$C_{20}H_{40}O_2$	[15]
139	Docosane	$C_{22}H_{46}$	[15]
Heterocyclics			
140	Oleamide	$C_{18}H_{35}NO$	[13]
141	Ethanolamine	C_2H_7NO	[13]
142	Uridine	$C_9H_{12}N_2O_6$	[13]
143	Uric acid	$C_5H_4N_4O_3$	[13]
144	Guanine	$C_5H_5N_5O$	[13]
145	Adenine	$C_5H_5N_5$	[13]
146	Spermidine	$C_7H_{19}N_3$	[13]
147	Putrescine	$C_4H_{12}N_2$	[13]
148	Ethylene glycol	$C_2H_6O_2$	[13]
149	Urea	CH_4N_2O	[13]
150	Allantoin	$C_4H_6N_4O_3$	[13]
151	Thymine	$C_5H_6N_2O_2$	[13]
152	2-(4-Hydroxy-3-methoxyphenyl)-ethanol	$C_9H_{12}O_3$	[13]
153	Dopamine	$C_8H_{11}NO_2$	[16]

tract and absorption of glucose via the membrane of the small intestine [23]. Subsequently, a research on the function of small intestine was implemented and it found that the *n*-butanol fraction with a dose of 50 mg/kg could improve the propulsive function of small intestine, and the mechanism of this action probably involves cholinergic nerve and nitric oxide [24].

Matsuda et al. found that momordin Ic inhibited gastric emptying in rats and inhibited glucose uptake in the small intestine *in vitro*, which contributed to the hypoglycemic action of momordin Ic [25]. Further study showed that momordin Ic inhibits gastric emptying in normal mice, hyperglycemic (including diabetic) and hypoglycemic mice, nonnutrient meal-loaded mice, and nutrient meal-loaded mice [3]. When gastric emptying is slow, the postprandial absorption of food will prolong. Hence, the inhibition of gastric emptying induced by momordin Ic may be useful for the prevention and treatment of diabetes and the morbid obesity with accelerated gastric emptying.
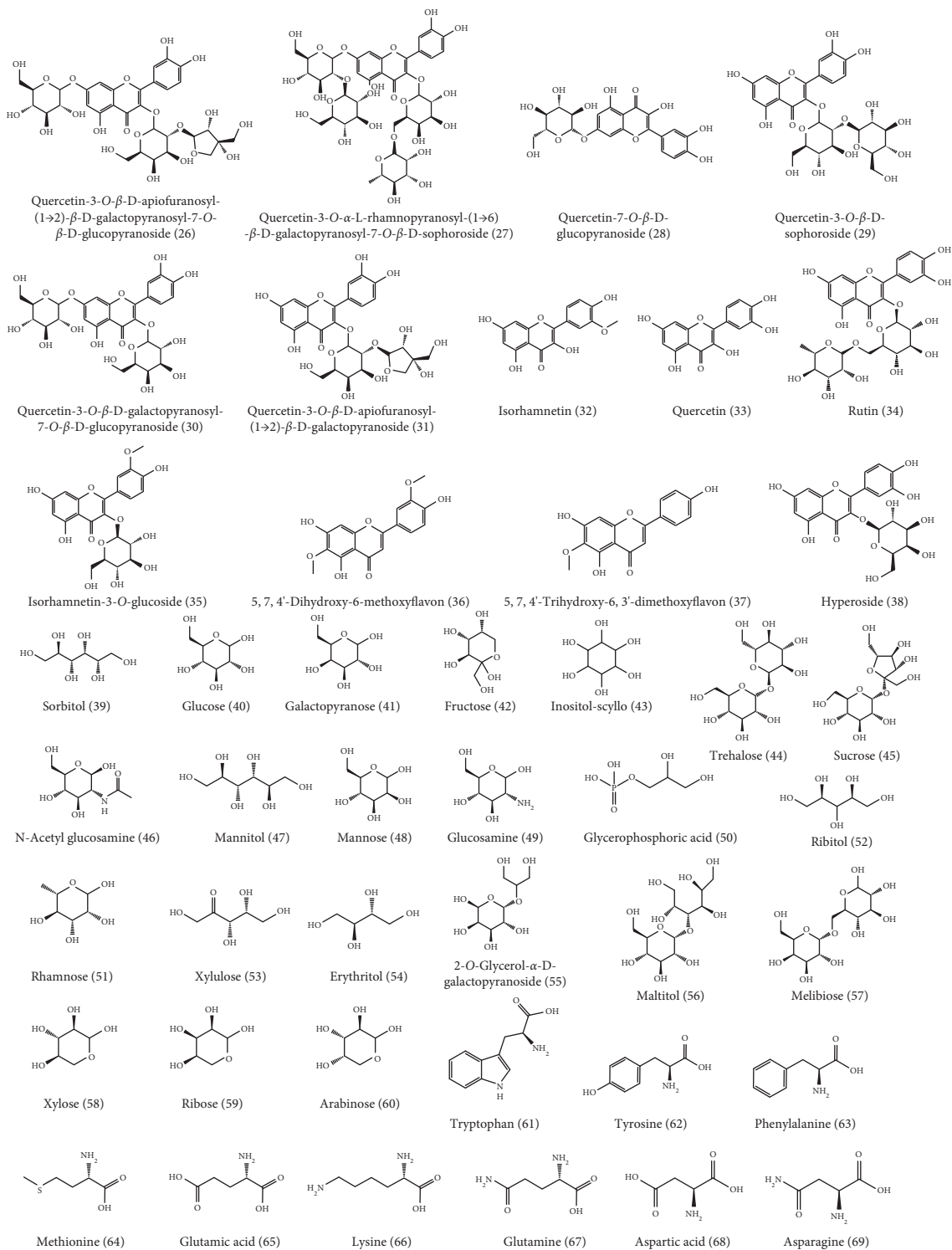
3.3. Anticancer Effect

3.3.1. Antiliver Cancer Effect. Momordin Ic was the main triterpenoid saponins within KF and has showed an antiliver cancer effect. Wang et al. have carried out a series of researches and found that HepG2 cells were sensitive to the cytotoxic effect of momordin Ic. Momordin Ic could induce apoptosis through oxidative stress-regulated mitochondrial dysfunction involving MAPK and PI3K-mediated iNOS and HO-1 pathways [26]. Based on these results, Wang et al. investigated the MAPK and PI3K pathways and their downstream proteins, such as PPARg and COX-2. Then, they provided the evidence that momordin Ic-induced HepG2 cell apoptosis was associated with PI3K and MAPK pathway-mediated PPARg activation [28]. In addition, Mi
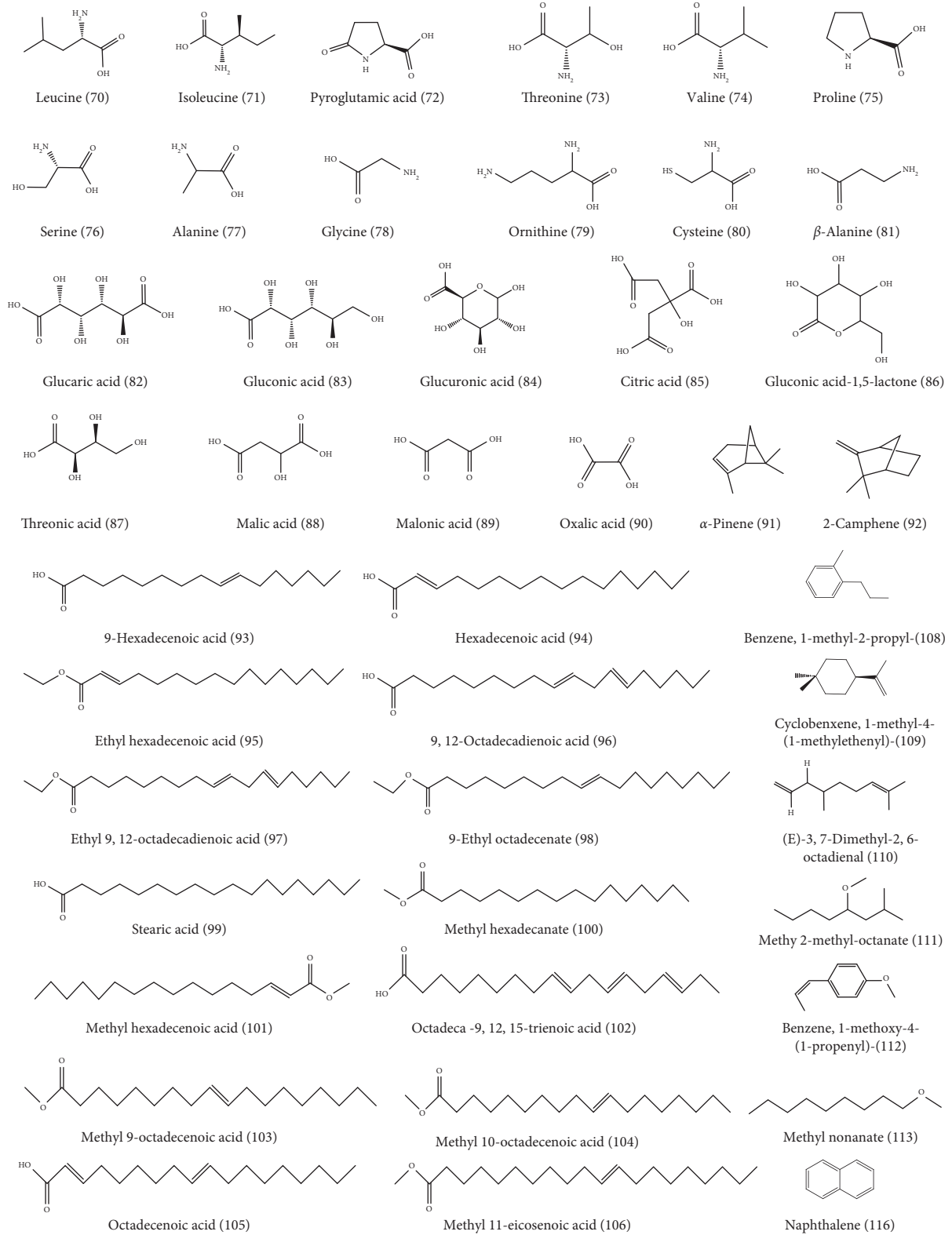
20-Hydroxyecdysone (1)

β-Sitosterol (2)

Momordin Ic (3)

Oleanic acid-3-O-β-D-xylopyranosly (1→3)
-β-D-glucopyranoside (4)

Momordin I (5)

Oleanolic acid (6)

Oleanolic acid-3-O-glucuronide (7)

Oleanolic acid-3-O-β-D-glucopyranoside (8)

28-O-Deglucosyl-chickusetsusaponin V (9)

2'-O-Glucopyranosyl-momordin Ic (10)

Chikusetsusaponin V (11)

Momordin IIc (12)

Kochianoside I (13)

Kochianoside II (14)

Kochianoside III (15)

Kochianoside IV (16)

Daucosterol (17)

Oleanolic acid-3-O-β-D-xylopyranosyl (1→3)
-β-D-glucopyranosiduronic acid 6-methyl ester (18)

3-O-β-D-glucuronopyranosy -28-O-β-D-
glucuronopyranosyl-oleanic-acid (19)

Oleanolic acid-3-β-D-glucopyranosiduronic
acid 6-methyl ester (20)

Stigmasterol -3-O-β-D-glucopyranoside (21)

6'-Methyl ester of momordin Ic (23)

Oleanic-acid-3-O-[β-D-glucopyranosyl (1→2) -β-D-
xylopyranosly (1→3)]-β-D-glucopyranosiduronic acid (22)

2'-O-β-D-Glucopyranosyl momordin Ic (24)

2'-O-β-D-Glucopyranosyl momordin IIc (25)

(a)

FIGURE 2: Continued.

Quercetin-3-O-β-D-apiofuranosyl-
(1→2)-β-D-galactopyranosyl-7-O-
β-D-glucopyranoside (26)

Quercetin-3-O-α-L-rhamnopyranosyl-(1→6)
-β-D-galactopyranosyl-7-O-β-D-sophoroside (27)

Quercetin-7-O-β-D-
glucopyranoside (28)

Quercetin-3-O-β-D-
sophoroside (29)

Quercetin-3-O-β-D-galactopyranosyl-
7-O-β-D-glucopyranoside (30)

Quercetin-3-O-β-D-apiofuranosyl-
(1→2)-β-D-galactopyranoside (31)

Isorhamnetin (32)

Quercetin (33)

Rutin (34)

Isorhamnetin-3-O-glucoside (35)

5, 7, 4'-Dihydroxy-6-methoxyflavon (36)

5, 7, 4'-Trihydroxy-6, 3'-dimethoxyflavon (37)

Hyperoside (38)

Sorbitol (39)

Glucose (40)

Galactopyranose (41)

Fructose (42)

Inositol-scyllo (43)

Trehalose (44)

Sucrose (45)

N-Acetyl glucosamine (46)

Mannitol (47)

Mannose (48)

Glucosamine (49)

Glycerophosphoric acid (50)

Ribitol (52)

Rhamnose (51)

Xylulose (53)

Erythritol (54)

2-O-Glycerol-α-D-
galactopyranoside (55)

Maltitol (56)

Melibiose (57)

Xylose (58)

Ribose (59)

Arabinose (60)

Tryptophan (61)

Tyrosine (62)

Phenylalanine (63)

Methionine (64)

Glutamic acid (65)

Lysine (66)

Glutamine (67)

Aspartic acid (68)

Asparagine (69)

(b)

Figure 2: Continued.

Leucine (70)

Isoleucine (71)

Pyroglutamic acid (72)

Threonine (73)

Valine (74)

Proline (75)

Serine (76)

Alanine (77)

Glycine (78)

Ornithine (79)

Cysteine (80)

β-Alanine (81)

Glucaric acid (82)

Gluconic acid (83)

Glucuronic acid (84)

Citric acid (85)

Gluconic acid-1,5-lactone (86)

Threonic acid (87)

Malic acid (88)

Malonic acid (89)

Oxalic acid (90)

α-Pinene (91)

2-Camphene (92)

9-Hexadecenoic acid (93)

Hexadecenoic acid (94)

Benzene, 1-methyl-2-propyl-(108)

Ethyl hexadecenoic acid (95)

9, 12-Octadecadienoic acid (96)

Cyclobenxene, 1-methyl-4-
(1-methylethenyl)-(109)

Ethyl 9, 12-octadecadienoic acid (97)

9-Ethyl octadecenate (98)

(E)-3, 7-Dimethyl-2, 6-
octadienal (110)

Stearic acid (99)

Methyl hexadecanate (100)

Methy 2-methyl-octanate (111)

Methyl hexadecenoic acid (101)

Octadeca -9, 12, 15-trienoic acid (102)

Benzene, 1-methoxy-4-
(1-propenyl)-(112)

Methyl 9-octadecenoic acid (103)

Methyl 10-octadecenoic acid (104)

Methyl nonanate (113)

Octadecenoic acid (105)

Methyl 11-eicosenoic acid (106)

Naphthalene (116)

(c)

Figure 2: Continued.

Methyl eicosenoic acid (107)

1-Undecyne (114)

Ethyl nonanoate (115)

Bicyclo (4, 3, 1) decan-10-one (117)

5-Ethyl-2-nonanol (118)

4, 8-Dimethyl-1-nonanol (119)

(Z)-β-Farnesene (120)

trans-β-Farnesene (121)

2, 6-Di-T-butyl-1, 4-benzoquinone (122)

β-Lonone (123)

Naphthalene, 1, 2, 3, 5, 6, 7, 8a-octahydro-1, 8a-demethyl-7-(1-methyethyl)-, [1R-(1α, 7β, 8aα)]-(124)

β-Chamigrene (125)

Ethyl dodecanoate (126)

Hexadecane (127)

Methyl tetradecanoate (128)

Benzene, 1, 1'-(1, 2-ethynediyl)bis-(129)

Octadecane (130)

Uridine (142)

2-Penddecanone, 6, 10, 14-trimetyl-(131)

Ethyl pentadecanoate (132)

Ethyl pentadecanoate (133)

Eicosane (134)

Methyl octadecadienoate (135)

Heneicosane (136)

Ethyl octadecadienoate (137)

Ethyl octadecanoate (138)

Docosane (139)

Ethanolamine (141)

Oleamide (140)

Uric acid (143)

Guanine (144)

Adenine (145)

Spermidine (146)

Putrescine (147)

Ethylene glycol (148)

Urea (149)

Allantoin (150)

Thymine (151)

2-(4-Hydroxy-3-methoxyphenyl)-ethanol (152)

Dopamine (153)

(d)

Figure 2: Chemical structures of substances within Kochiae Fructus.

TABLE 2: Traditional uses of Kochiae Fructus (KF) referring to database "https://www.yaozh.com."

Traditional uses	Reference
KF is used to treat frequent urination, urinary incontinence, and abnormal leucorrhea and has an effect of strengthening ears	Ben Cao Qiu Yuan
KF is used to treat frequent urination and urinary incontinence and has an effect of strengthening ears	Ben Cao Qiu Zhen
KF has an effect of heat-clearing	Ben Cao Shu
KF is used to treat skin itching and eczema and has effects of reducing swelling and improving eyesight and ears	Yao Jian
KF is good for urinating and has effects of improving eyesight and ears and antiaging	Ben Jing
KF is used to treat eczema	Bie Lu
KF has an effect for urinating	Ben Cao Zheng Yi
KF is used to treat male impotence	Yao Xing Lun
KF has an effect of reducing swelling	Ri Hua Zi Ben Cao
KF is used to improve urination problems, treat rubella, and abnormal vaginal discharge	Dian Nan Ben Cao
KF is used to treat itchy skin	Ben Cao Yuan Shi
KF can help urination	Ben Cao Bei Yao
KF is used to treat swelling and pain of the head and eyes, back pain, blood in the stool, and malignant sores	Yu Qiu Yao Jie

et al. showed that the underlying mechanisms of the cross-talk between apoptosis and autophagy involved ROS-related PI3K/Akt, MAPK, and NF-κB signaling pathways, and momordin Ic simultaneously induced apoptosis and autophagy by activating these intersecting signaling pathways [27]. The summarized signal pathway is presented in Figure 3. On the contrary, momordin Ic showed a good anti-invasive activity by altering E-cadherin, VCAM-1, ICAM-1, and MMP-9, and the underlying mechanism involved PPARγ activation and COX-2 inhibition [30].

3.3.2. Antiprostate Cancer Effect. The MeOH extract of KF has shown inhibition effects on human umbilical vein endothelial cell angiogenesis and human prostate cancer cell proliferation [31]. As a member of the de-SUMOylation protease family, SUMO-specific protease 1 (SENP1) is elevated in prostate cancer (PCa) cells and is involved in PCa pathogenesis [43–46]. Momordin Ic as a novel SENP1 inhibitor could inhibit proliferation of prostate cancer cells *in vitro* and *in vivo* by inducing cell cycle arrest and apoptosis [32]. The possible mechanism is that momordin Ic could increase the sub-G1 phase cell population, increase numbers of annexin-V positive cells, increase active caspase-3, caspase-8, and PARP1 cleavage, and reduce cyclin B and CDK1 levels. Thus, it was considered that SENP1 may play an important role in momordin Ic-induced cell death in prostate cancer cells, even though the downstream effectors of SENP1 that mediate momordin Ic-induced apoptosis are currently unknown.

3.4. Antifungal Effect. In vitro, the water extract of KF showed a strong inhibition on common dermatophytes. Its minimum inhibitory concentration (MIC) on *Trichophyton mentagrophytes* was 3.12% and on *Trichophyton rubrum*, *Microsporum canis*, *Trichophyton violaceum*, and *Trichophyton schoenleinii* were 0.78% [33]. Wu et al. tested six KF extracts against *Fusarium graminearum*, *Fusarium oxysporum*, *Monilia cinerea*, *Physalos porapiricola*, *Alternaria alternata*, and *Valsa mali*. As a result, the water extract had the strongest

inhibition effect on all six plant pathogenic bacteria with antifungal activities of more than 74.34%, and the water, petroleum ether, chloroform, ethylacetate, and methanol extracts showed stronger antifungal activities against *Monilia cinerea* and *Valsa mali* than the others [34]. In addition, the saponin extract, flavone extract I (40% alcohol eluent), flavone extract II (80% alcohol eluent), and lipid extract from KF were tested against *Microsporum ferrugineum*, *Microsporum gypseum*, *Trichophyton schoenleini*, *Trichophyton mentagrophytes*, *Trichophyton violaceum*, *Trichophyton rubrum*, *Epidermophyton floccosum*, *Aspergillus fumigatus*, *Candida albicans*, and *Cryptococcus neoformans*. The lipid extract showed a good antifungal effect on *Microsporum ferrugineum*, *Microsporum gypseum*, *Trichophyton mentagrophytes,* and *Trichophyton rubrum*; the saponin extract gave inhibition effects on *Microsporum ferrugineum*, *Microsporum gypseum*, *Trichophyton schoenleini*, *Trichophyton mentagrophytes,* and *Trichophyton rubrum*; the flavone extract I (40% alcohol eluent) exerted inhibition effects on *Microsporum ferrugineum*, *Trichophyton rubrum,* and *Epidermophyton floccosum*, whereas the flavone extract II (80% alcohol eluent) play an inhibitory role on *Microsporum ferrugineum*, *Microsporum gypseum,* and *Trichophyton rubrum*. Unfortunately, the MIC was not mentioned in this article [35]. Above all, this effect of KF supports its traditional use in gynecological infection.

3.5. Antipruritogenic Effect. The 70% ethanol extract (200 mg/kg) and methanol extract of KF (500 mg/kg) have been proved to inhibit the scratching behavior on a compound 48/80-induced pruritogenic model in male ddY mice [36]. Momordin Ic isolated from KF also exhibited an inhibition effect at a dose of 50 mg/kg. Meanwhile, in an itching guinea pig model and an itching mice model, the water extract of KF at the concentration of 0.15 g/mL could significantly decrease the number of itching and total time of itching within 30 minutes, indicating that KF could be used as an antipruritogenic agent [33]. These results agree with the traditional use of KF for itch.

TABLE 3: Pharmacological effects of Kochiae Fructus (KF).

Pharmacological effect	Model	Administration	Minimal active concentration	Reference
Anti-inflammatory effect	The ddY mice in an acetic acid-induced vascular permeability	Tested drug: 70% ethanol extract of KF at the doses of 50, 200, and 500 mg/kg, p.o. Positive control: indomethacin at 10 mg/kg	200 mg/kg	[19]
	The ddY mice in a carrageenin-induced edema	Tested drug: 70% ethanol extract of KF at the doses of 50, 200, and 500 mg/kg, p.o. Positive control: indomethacin at 10 mg/kg	200 mg/kg	[19]
	The ddY mice in a compound 48/80-induced edema	Tested drug: 70% ethanol extract of KF at the doses of 50, 200, and 500 mg/kg, p.o. Positive control: diphenhydramine at 50 mg/kg	500 mg/kg	[19]
	The ddY mice in a chemical mediator-induced edema	Tested drug: 70% ethanol extract of KF at the doses of 50, 200, and 500 mg/kg, p.o. Positive control: cyproheptadine at 2 mg/kg; diphenhydramine at 50 mg/kg	200 mg/kg	[19]
	The isolated ileum of guinea pig in a histamine-induced contraction	Tested drug: 70% ethanol extract of KF at the doses of 10, 50, 100, and 300 μg/mL	220 μg/mL	[19]
	The ddY mice in an arachidonic acid-induced edema	Tested drug: 70% ethanol extract of KF at the doses of 50, 200, and 500 mg/kg, p.o. Positive control: phenidone at 20 mg/kg, i.v.	500 mg/kg	[19]
	A picryl chloride-induced ear inflammatory model in ICR mice	Tested drug: 70% ethanol extract of KF at the doses of 100, 200, and 500 mg/kg, i.g. Positive control: prednisone at 50 mg/kg	500 mg/kg	[20]
	A dinitrochlorobenzene-induced allergic contact dermatitis model in rats	Tested drug: total flavonoids of KF at the doses of 100 and 200 mg/kg. p.o. Positive control: sodium prednisolone acetate at 2.5 μg/mL	100 mg/kg	[21]
	A DNFB-induced contact dermatitis model in mice	Tested drug: methanol extract of KF at the doses of 30, 100, and 300 μg/ear for external use Positive control: dexamethasone at 75 μg/ear	100 μg/ear	[22]
	The ddY mice in a carrageenin-induced edema	Tested drug: momordin Ic at the doses of 20, 50, and 100 mg/kg, p.o. Positive control: indomethacin at 10 mg/kg	20 mg/kg	[19]
	LPS-stimulated RAW 264.7 cell line	Tested drug: 20-hydroxyecdysone, momordin Ic, and oleanolic acid with various concentrations (6.25, 12.5, or 25 μM) Positive control: indomethacin at 2.5 ng/mL	6.25 μM	[5]

TABLE 3: Continued.

Pharmacological effect	Model	Administration	Minimal active concentration	Reference
Hypoglycemic effect				
	Normal, alloxan-induced hyperglycemic and insulin-induced hypoglycemic mice	Tested drug: n-butanol extract of KF at the doses of 25 and 50 mg/kg, p.o.	25 mg/kg	[23]
	Examining the activity of α-glucosidase in rat intestine in vitro	Tested drug: n-butanol extract of KF at the doses of 62.5, 125, 250, and 500 μg/mL. Positive control: acarbose at 2 μg/mL	125 μg/mL	[23]
	Examining the ability of glucose absorption in rat intestine in vitro	Tested drug: n-butanol extract of KF at the doses of 0, 100, 200, 400, and 800 μg/mL	100 μg/mL	[23]
	Testing the propulsive function of small intestine in normal, fenfluramine-treated, dopamine-treated, acetic acid-treated, and Nω-nitro-L-arginine-treated rats	Tested drug: n-butanol extract of KF at the doses of 25 and 50 mg/kg, p.o.	50 mg/kg	[24]
	Testing the gastric emptying in rats	Tested drug: oleanolic acid 3-O-glucuronide and momordin Ic at the doses of 12.5, 25, and 50 mg/kg, p.o. Positive control: atropine sulfate at 10 mg/kg	25 and 12.5 mg/kg, respectively	[25]
	Testing the glucose uptake in rat small intestine in vitro	Tested drug: oleanolic acid 3-O-glucuronide and momordin Ic at the doses of 0, 5, 50, and 500 μM. Positive control: phlorizin at 1 μM	50 and 5 μM, respectively	[25]
	Gastric emptying test on 1.5% carboxymethyl cellulose sodium salt test meal-loaded mice, 40% glucose test meal-loaded mice, milk test meal-loaded mice, and 60% ethanol test meal-loaded mice	Tested drug: momordin Ic in the dose range of 12.5–50 mg/kg, p.o.	50 mg/kg	[3]
Anticancer effects				
	Inducing apoptosis of human hepatocyte carcinoma HepG2 cells	Tested drug: momordin Ic in the concentration range of 10–30 μM	15 μM	[26]
	Inducing autophagy of human hepatocyte carcinoma HepG2 cells	Tested drug: momordin Ic in the dose range of 5–20 μM	10 μM	[27]
Antiliver cancer	Inducing apoptosis of human hepatocyte carcinoma HepG2 cells	Tested drug: momordin Ic in the dose range of 5, 10, and 15 μM	5 μM	[28]
	Suppressing invasion of human hepatocyte carcinoma HepG2 cells	Tested drug: momordin Ic at the dose of 10 μM	10 μM	[29]
	Inhibiting migration and invasion of human hepatocyte carcinoma HepG2 cells	Tested drug: momordin Ic in the dose range of 1–10 μM	5 μM	[30]
Antiprostate cancer	VEGF-induced angiogenesis in human umbilical vein endothelial cells and proliferation in prostate cancer cells	Tested drug: methanol extract of KF in the dose range of 10–20 μg/mL and 10–250 μg/mL, respectively	20 μg/mL and 100 μg/mL, respectively	[31]
	Testing the SUMO-specific protease 1 in prostate cancer cells and a xenograft PC3 tumor mouse model	Tested drug: momordin Ic at the dose of 6.25, 12.5, and 25 μM and 10 mg/kg/day, i.p. For 20 days, respectively	IC$_{50}$ was 15.37 μM and 10 mg/kg/day	[32]

TABLE 3: Continued.

Pharmacological effect	Model	Administration	Minimal active concentration	Reference
Antifungal effect				
	In vitro for *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Microsporum canis*, *Trichophyton violaceum*, and *Trichophyton schoenleinii*	Tested drug: water extract of KF in the concentration range of 0.04%–25%	3.12%	[33]
	Inhibiting the growing of *Fusarium graminearum*, *Fusarium oxysporum*, *Monilia cinerea*, *Physalos porapiricola*, *Alternaria alternata*, and *Valsa mali*	Tested drug: water, petroleum ether, chloroform, ethylacetate, and methanol extract of *KF* with the concentration of dose 1 mg/15 mL	1 mg/15 mL	[34]
	In vitro for *Microsporum ferrugineum*, *Microsporum gypseum*, *Trichophyton schoenleini*, *Trichophyton mentagrophytes*, *Trichophyton violaceum*, *Trichophyton rubrum*, *Epidermophyton floccosum*, *Aspergillus fumigatus*, *Candida albicans*, *Cryptococcus neoformans*	Tested drug: the saponin extract, flavone extract I (40% alcohol eluent), flavone extract II (80% alcohol eluent), and lipid extract with no concentration mentioned	All samples have the antifungal effect on *Microsporum ferrugineum and Trichophyton rubrum*, but the concentration was not mentioned	[35]
Antipruritogenic effect				
	A compound 48/80-induced pruritogenic model in male ddY mice	Tested drug: 70% ethanol extract of KF at the dose of 200 and 500 mg/kg, p.o.	200 mg/kg	[36]
		Tested drug: methanol extract of KF at the dose of 50, 200, and 500 mg/kg, p.o.	500 mg/kg	
		Tested drug: momordin Ic at the dose of 20, 50, and 100 mg/kg, p.o. Positive control: diphenhydramine at 20 mg/kg	50 mg/kg	
	Itching guinea pig model caused by histamine itching mice model	Tested drug: water extract of KF at the concentration of 0.15 g/mL, 0.3 g/mL, and 0.6 g/mL for external use Positive control: cyproheptadine	0.15 g/mL	[33]
Antinociceptive effect				
	The ddY mice in an acetic acid-induced writhing test	Tested drug: 70% ethanol extract of KF at the dose of 50, 200, and 500 mg/kg, p.o.	500 mg/kg	[19]
		Tested drug: momordin Ic at the dose of 20, 50, and 100 mg/kg, p.o. Positive control: aspirin at 200 mg/kg	20 mg/kg	
Inhibition effect on hypersensitivity				
	DTH models upon challenge with SRBC or PC	Tested drug: 70% ethanol extract of KF at the dose of 100, 200, and 500 mg/kg. Positive control: prednisone at 50 mg/kg	100 mg/kg	[20]
		Tested drug: total saponins extract of KF at the dose of 50, 100, and 200 μg/mL Positive control: cyproheptadine at 20 mg/kg	200 mg/kg	
Myocardial protection				
	A furazolidone-induced dilated cardiomyopathy model in Wistar rats	Tested drug: water extract of KF at the dose of 5 and 20 mg/g, p.o. Negative model: water	20 mg/g	[37]

Pharmacological effect	Model	Administration	Minimal active concentration	Reference
Hepatoprotective effect				
	Carbon tetrachloride-induced liver damage in rats	Tested drug: momordin Ic and oleanolic acid at the dose of 30 mg/kg/day for 14 days, p.o. Negative control: saline	30 mg/kg/day for 14 days	[38]
Protecting gastric mucosal lesions				
	Ethanol-induced gastric mucosal lesions in rats and indomethacin-induced gastric mucosal lesions in rats	Tested drug: momordin Ic in the dose range of 2.5–50 mg/kg, p.o. Positive control: omeprazole at 20 or 5 mg/kg, respectively	5 mg/kg	[39]
Suppressing osteoclastogenesis				
	A cocultured system and a RANKL-induced osteoclast precursor system	Tested drug: momordin Ic in the dose range of 0.1–5 μM	0.5 μM	[40]
Antibacteria effect				
	Minimum inhibitory concentration (MIC) test on *Escherichia coli*	Tested drug: oleanolic acid in the dose range of 15.6–4000 μg/mL	31.3 μg/mL	[41]
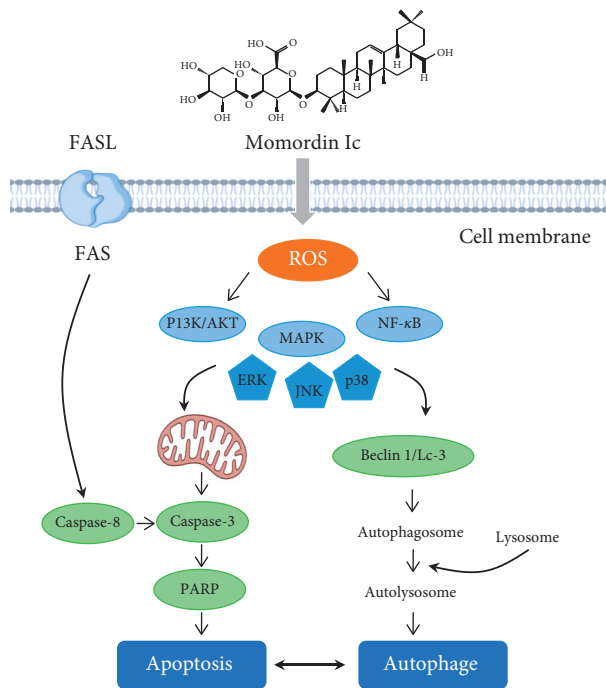
FIGURE 3: The signal pathways of antiliver cancer effect of momordin Ic.

3.6. Others. The inhibition effect of hypersensitivity of 70% ethanol and total saponin extracts from KF has been tested on DTH models upon challenge with SRBC or PC. As a result, the 70% ethanol extract produced a concentration-dependent reduction on immediate and delayed-type hypersensitivity, while total saponins extract showed an inhibitory tendency at 200 mg/kg [20]. This effect might have a close relationship with its stabilization of mast cell membrane, reduction of release of anaphylactic mediators, and anti-inflammatory activities [20]. The water extract of KF at the dose of 20 mg/g could reverse the imbalance of Th1/Th2 cell in rat model with dilated cardiomyopathy, which

reduced the damage of immune response to myocardium and protected the heart function. Momordin Ic gave a protective effect on gastric mucosal lesions [37]. Kim et al. discovered that momordin Ic has a hepatoprotective effect against CCl$_4$-induced liver damage because it could enhance the hepatic antioxidant defense system [38]. Meanwhile, as an AP-1 inhibitor, momordin Ic could downregulate NF-κB activation as well as AP-1 activation, which plays a key role in osteoclast differentiation, by inhibiting IκB degradation and c-Fos expression, respectively. Therefore, momordin Ic has high potential to be a good candidate for controlling bone disorders in the future [40]. In addition, the extracts of KF, including total flavonoid, saponin, and phenolic, were proved to have a good antioxidant activity by measuring free radical scavenging activities with ABTS, DPPH, or FARP assay [47–50]. Scavenging free radicals play a key role in aging and inflammation [51]. Therefore, its antioxidant effects need to be further studied on these aspects.

The studies on toxicity of KF are scarce. Although KF is almost nontoxic in traditional use, the animal death was found when a large dosage is used. According to a toxicological study, when KM mice were orally administrated with water extract of KF in a dose range from 4.5 mg/kg to 9.4 mg/kg, the median lethal dose (LD$_{50}$) was 7.15 ± 0.03 g/kg [35]. Therefore, the toxic and side effects of KF should be paid more attention in its clinical application.

4. Quality Control

The quality of herbal medicines is the key for its clinical efficacy and safety, and hence, establishing a quality control system is the premise of its clinical application. The quality control of KF was focused on quantitative analysis of components by a series of analytical methods, such as ultraviolet-visible detector (UV), gas chromatography-mass spectrometry (GC-MS), and high-performance liquid chromatography-evaporative light scattering detector (HPLC-ELSD). Since the main component of KF is triterpenoid saponin, whose UV absorption is poor,

researchers incline to use ELSD. Xia et al. developed a method to determine the content of momordin Ic in KF and the content of momordin Ic was 0.83%–0.21% in four kinds of marketed KF [52]. Moreover, they used HPLC-ELSD and colorimetric methods to determine the content of momordin Ic and total saponins, respectively, in KF at different collecting times or from eleven places in China [53, 54]. Except for saponin, there also established an HPLC method with good stability and reproducibility to simultaneously determine the content of rutin and quercetin in KF [55]. Currently, the fingerprint derived from HPLC has been an acknowledged method to control the quality of traditional Chinese medicine and botanical medicine. An HPLC fingerprint method was applied to 10 batches of KF purchased from Shandong, China. According to the cluster analysis, 19 common peaks of fingerprint were found, and 10 batches could be divided into 3 groups related to their origins [56]. The results showed that this method could differentiate samples from different geographical origins or processing methods. Nevertheless, there were few compounds quantified as mark compounds for the quality control of KF, and it is in urgent need of a comprehensive quantification method to further ensure the quality control.

5. Pharmacokinetics

Momordin Ic is a representative pharmacologically active ingredient and quality control marker of KF, and its pharmacokinetic property has attracted attentions. Yan et al. developed and validated a highly selective and sensitive method based on ultraperformance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) for routine analysis of momordin Ic in rat plasma. After intravenous administration of momordin Ic at 0.52, 1.56, and 4.67 mg/kg in rats, the AUC_{last} (area under the concentration-time curve from time 0 to t hours postodose) values were 1864.17 ± 431.01, 5466.00 ± 889.86, and 16890.45 ± 3028.64 ng·h/mL, respectively, which was consistent with linear pharmacokinetic characteristics. The elimination half-life ($t_{1/2}$) values were 1.22 ± 0.39, 1.14 ± 0.10, and 1.83 ± 0.39 h, respectively [4]. However, there are few studies on the pharmacokinetic of other substances within KF and on the interaction between substances during their ADME *in vivo*.

6. Conclusion and Perspectives

Recent pharmacology studies showed anti-inflammatory, antifungal, antiallergic, and antipruritogenic effects of KF, which supports the traditional clinical applications including the treatment of diseases in the skin, eye, and urinary tract in China, Korea, and Japan. Interestingly, the anticancer, hypoglycemic, and hepatoprotective effects of KF were also tested. Besides, the potential mechanisms of some effects were also elucidated. However, there are few toxicology studies on KF, which may be necessary for its better application as a medicine or a food. A total of 25 triterpenoids, 13 flavonoids, 22 carbohydrates, 21 amino acids, 9 organic acid, 49 essential oils, and 14 heterocyclics within KF have been reported. Momordin Ic is a main substance, and it is usually used as a phytochemical marker for the quality control of KF. The pharmacological effects were achieved by the chemical constituents within KF. Hence, the interrelationship between compounds and pharmacological activities should be further studied. The pharmacokinetics of KF was lack, and a range of pharmacokinetic studies on its active compounds are needed to provide comprehensive data for clinical application. Altogether, this review extensively summarized phytochemistry, pharmacology, toxicity, quality control, and pharmacokinetic studies on KF to provide information for its further research and clinical applications.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Disclosure

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Authors' Contributions

Wei Zou and Zhong Tang contributed equally.

Acknowledgments

References

[1] Flora of China Editorial Committee and the Chinese Academy of Sciences, *Flora of China*, Beijing Science Press, Beijing, China, 1986.

[2] L. I. Pei-Yuan, H. Li-Ni, S. U. Wei, D. Ling-Yu, P. Mei-Ping, and Z. Zhi-Xiang, "Radical scavenging activity and total phenolics content of Kochia scoparia," *Hub Agricultural Ences*, vol. 55, no. 11, pp. 2899–2901, 2016.

[3] H. Matsuda, Y. Li, J. Yamahara, and M. Yoshikawa, "Inhibition of gastric emptying by triterpene saponin, momordin Ic, in mice: roles of blood glucose, capsaicin-sensitive sensory nerves, and central nervous system," *Journal of Pharmacology and Experimental Therapeutics*, vol. 289, no. 2, pp. 729–734, 1999.

[4] H. Yan, Y. Song, W. Zhou, and S. Zhang, "A selective and sensitive method based on UPLC-MS/MS for quantification of momordin Ic in rat plasma: application to a pharmacokinetic study," *Journal of Pharmaceutical and Biomedical Analysis*, vol. 115, pp. 196–200, 2015.

[5] S. R. Yoo, S. J. Jeong, N. R. Lee, H. K. Shin, and C. S. Seo, "Quantification analysis and in vitro anti-inflammatory effects of 20-hydroxyecdysone, momordin Ic, and oleanolic acid

from the fructus of Kochia scoparia," *Pharmacognosy Magazine*, vol. 13, no. 51, pp. 339–344, 2017.

[6] L. U. Xiang-Hong, X. U. Xiang-Dong, F. U. Hong-Wei, B. Chen, J. K. Tian, and L. Zhang, "Study on chemical constituents of Kochia scoparia," *Journal of Chinese Medicinal Materials*, vol. 36, no. 6, pp. 921–924, 2012.

[7] H. Matsuda, Y. Dai, Y. Ido et al., "Studies on Kochiae Fructus. V. Antipruritic effects of oleanolic acid glycosides and the structure-requirement," *Biological & Pharmaceutical Bulletin*, vol. 21, no. 11, pp. 1231–1233, 1998.

[8] M. Yoshikawa, Y. Dai, H. Shimada et al., "Studies on Kochiae Fructus. II. On the Saponin constituents from the fruit of Chinese Kochia Scoparia (Chenopodiaceae): chemical structures of Kochianosides I, II, III, and IV," *Chemical & Pharmaceutical Bulletin*, vol. 45, 2010.

[9] W. Hao, F. Chun-Lin, W. Bei, D. Yue, and Y. E. Wen-Cai, *Triterpene and Saponins from Kochia Scoparia*, Chinese Journal of Natural Medicines, Beijing, China, 2003.

[10] X. U. Yun-Hui, H. Huang, Z. X. Guo, N. Zhang, D. Y. Kong, and M. L. Hua, *Chemical Constituents of Antifungal Extract from Kochiae Fructus*, Chinese Traditional Patent Medicine, Beijing, China, 2012.

[11] Y. Wen, Y. Chen, Z. Cui, J. Li, and Z. Wang, "Triterpenoid glycosides from the fruits ofKochia scoparia," *Planta Medica*, vol. 61, no. 5, pp. 450–452, 1995.

[12] Y.-H. Xu, H. Huang, N. Zhang, D.-Y. Kong, and M.-L. Hua, "Studies on the flavone glycosides from fructus kochiae," *Journal of Asian Natural Products Research*, vol. 16, no. 2, pp. 141–147, 2014.

[13] A. J. Houlihan, P. Conlin, and J. C. Chee-Sanford, "Water-soluble exudates from seeds of Kochia scoparia exhibit antifungal activity against Colletotrichum graminicola," *PLoS One*, vol. 14, no. 6, 2019.

[14] M. Yang, J. Li, J. Cai, and S. Yang, "Supercritical CO_2 extraction and GC-MS analysis of Kochia Fructus oil," *Zhong Yao Cai*, vol. 26, no. 7, p. 494, 2003.

[15] Y. Wen, Z. Wang, and C. Xu, "Study on the constituents of essential oil from Kochiae Fructus," *Zhong Yao Cai*, vol. 1, no. 2, pp. 29–31, 1992.

[16] J. B. Chang, M. E. Lane, M. Yang, and M. Heinrich, "A hexaherbal TCM decoction used to treat skin inflammation: an LC-MS-based phytochemical analysis," *Planta Medica*, vol. 82, no. 11-12, pp. 1134–1141, 2016.

[17] N. Ma and X. Ma, "Dietary amino acids and the gut-microbiome-immune Axis: physiological metabolism and therapeutic prospects," *Comprehensive Reviews in Food Science and Food Safety*, vol. 18, no. 1, pp. 221–242, 2019.

[18] Y. Zhang, R. Wang, C. Wang, and S. Bao, "Research pregress on traditional Chinese medicine Kochia scoparia (L.) Schrad," *Chinese Medicine Journal of Research and Practice*, vol. 30, no. 1, pp. 84–86, 2016.

[19] H. Matsuda, Y. Dai, Y. Ido, M. Yoshikawa, and M. Kubo, "Studies on kochiae fructus. IV. Anti-allergic effects of 70% ethanol extract and its component, momordin Ic from dried fruits of Kochia scoparia L," *Biological & Pharmaceutical Bulletin*, vol. 20, no. 11, pp. 1165–1170, 1997.

[20] Y. Dai, Y. F. Xia YufengXia, and H. B. Chen HaibiaoChen, "Inhibition of lmmediate and delayed type hypersensitivity by the 70% ethanolic extract from Fructus Kochiae Scopariae," *Chinese Journal of Modern Applied Pharmacy*, vol. 18, 2001.

[21] Z. Xiao, S. Xiao, Y. Zhang, T. Pan, and B. Ouyang, "The anti-inflammatory effect of fructus kochiae on allergic contact dermatitis rats via pERK1/2/TLR4/NF-κB pathway

activation," *Evidence-Based Complementary and Alternative Medicine*, vol. 4, Article ID 1096920, 2018.

[22] S. Jo, J. Ryu, H.-Y. Han, G. Lee, M. H. Ryu, and H. Kim, "Anti-inflammatory activity of Kochia scoparia fruit on contact dermatitis in mice," *Molecular Medicine Reports*, vol. 13, no. 2, pp. 1695–1700, 2016.

[23] D. Yue, X. Yufeng, and L. Silong, "Studies on the hypoglycemic mechanism of n-butanol fraction from Fructus Kochiae (地肤子)," *Pharmacology and Clinics of Chinese Materia Medica*, vol. 19, 2003.

[24] D. Yue, X. Yufeng, and Y. Li, "Effect of n-butanol fraction from Fructus Kochiae(地肤子) on intestinal motility," *Pharmacology\s&\sclinics of Chinese Materia Medica*, vol. 20, 2004.

[25] H. Matsuda, Y. Li, T. Murakami, N. Matsumura, J. Yamahara, and M. Yoshikawa, "Antidiabetic principles of natural medicines. III. Structure-related inhibitory activity and action mode of oleanolic acid glycosides on hypoglycemic activity," *Chemical & Pharmaceutical Bulletin*, vol. 46, no. 9, pp. 1399–1403, 1998.

[26] J. Wang, L. Yuan, H. Xiao, C. Xiao, Y. Wang, and X. Liu, "Momordin Ic induces HepG2 cell apoptosis through MAPK and PI3K/Akt-mediated mitochondrial pathways," *Apoptosis*, vol. 18, no. 6, pp. 751–765, 2013.

[27] Y. Mi, C. Xiao, Q. Du, W. Wu, G. Qi, and X. Liu, "Momordin Ic couples apoptosis with autophagy in human hepatoblastoma cancer cells by reactive oxygen species (ROS)-mediated PI3K/Akt and MAPK signaling pathways," *Free Radical Biology and Medicine*, vol. 90, pp. 230–242, 2016.

[28] J. Wang, L. Yuan, H. Xiao et al., "A novel mechanism for momordin Ic-induced HepG2 apoptosis: involvement of PI3K- and MAPK-dependent PPARγ activation," *Food & Function*, vol. 5, no. 5, pp. 859–868, 2014.

[29] J. Wang, Y. Han, M. Wang, Q. Zhao, X. Chen, and X. Liu, "Natural triterpenoid saponin Momordin Ic suppresses HepG2 cell invasion via COX-2 inhibition and PPARγ activation," *Toxicol In Vitro*, vol. 65, Article ID 104784, 2020.

[30] J. Wang, Q. Liu, H. Xiao, X. Luo, and X. Liu, "Suppressive effects of Momordin Ic on HepG2 cell migration and invasion by regulating MMP-9 and adhesion molecules: involvement of p38 and JNK pathways," *Toxicology in Vitro*, vol. 56, pp. 75–83, 2019.

[31] H.-D. Cho, J.-H. Kim, J.-K. Park, S.-M. Hong, D.-H. Kim, and K.-I. Seo, "Kochia scoparia seed extract suppresses VEGF-induced angiogenesis via modulating VEGF receptor 2 and PI3K/AKT/mTOR pathways," *Pharmaceutical Biology*, vol. 57, no. 1, pp. 684–693, 2019.

[32] J. Wu, H. Lei, J. Zhang et al., "Momordin Ic, a new natural SENP1 inhibitor, inhibits prostate cancer cell proliferation," *Oncotarget*, vol. 7, no. 37, pp. 58995–59005, 2016.

[33] J. N. Wang, Q. Y. Liu, C. H. Yao et al., "[Normative research on bacteriostasis and relieving itching external therapeutic function of kochiae fructus]," *Zhong Yao Cai*, vol. 35, no. 12, pp. 1974–1977, 2012.

[34] J. Wu, S. Guang-Lub, S. U. Xue-Youa, W. Zhe-Yia, and W. You-Niana, *A Preliminary Study On Bioactivity Of Extracts From Fructus Kochiae Against Several Phytopathogens*, Journal of Beijing University of Agriculture, Beijing, China, 2008.

[35] Y. Wang and C. Sui, "Pharmacology and toxicity comparation of difuzi and Li," *Journal of Modern Applied Pharmacy*, vol. 12, no. 4, pp. 10–12, 1995.

[36] M. Kubo, H. Matsuda, Y. Dai, Y. Ido, and M. Yoshikawa, "[Studies on Kochiae Fructus. I. Antipruritogenic effect of

70% ethanol extract from kochiae fructus and its active component]," *Yakugaku Zasshi*, vol. 117, no. 4, pp. 193–201, 1997.

[37] D. Le, Z. Jiarong, and B. Yonghong, "The regulatory effect of fructus kochiae on Th cell activity in rats with dilated cardiomyopathy," *Jiangsu Medical Journal*, vol. 38, 2012.

[38] N.-Y. Kim, M.-K. Lee, M.-J. Park et al., "Momordin Ic and oleanolic acid from Kochiae Fructus reduce carbon tetrachloride-induced hepatotoxicity in rats," *Journal of Medicinal Food*, vol. 8, no. 2, pp. 177–183, 2005.

[39] H. Matsuda, Y. Li, T. Murakami, J. Yamahara, and M. Yoshikawa, "Protective effects of oleanolic acid oligoglycosides on ethanol- or indomethacin-induced gastric mucosal lesions in rats," *Life Sciences*, vol. 63, no. 17, pp. PL245–PL250, 1998.

[40] Y. H. Hwang, J. W. Lee, E.-R. Hahm et al., "Momordin I, an inhibitor of AP-1, suppressed osteoclastogenesis through inhibition of NF-κB and AP-1 and also reduced osteoclast activity and survival," *Biochemical and Biophysical Research Communications*, vol. 337, no. 3, pp. 815–823, 2005.

[41] M. Yan, W. Zhang, G. Luo, S. Demetra, X. Wang, and C. Chen, "Screening of antibacterial active constituents from fructus kochiae," *Chemistry & Bioengineering*, vol. 36, no. 2, pp. 28–31, 2019.

[42] Z. Xiao, S. Xiao, Y. Zhang, T. Pan, and B. Ouyang, "The anti-inflammatory effect of fructus kochiae on allergic contact dermatitis rats via pERK1/2/TLR4/NF-kappaB pathway activation," *Evidence-Based Complementary and Alternative Medicine*, vol. 2018, Article ID 1096920, 12 pages, 2018.

[43] T. Bawa-Khalfe, J. Cheng, Z. Wang, and E. T. H. Yeh, "Induction of the SUMO-specific protease 1 transcription by the androgen receptor in prostate cancer cells," *Journal of Biological Chemistry*, vol. 282, no. 52, pp. 37341–37349, 2007.

[44] J. Cheng, X. Kang, S. Zhang, and E. T. H. Yeh, "SUMO-specific protease 1 is essential for stabilization of HIF1α during hypoxia," *Cell*, vol. 131, no. 3, pp. 584–595, 2007.

[45] T. Bawa-Khalfe, J. Cheng, S.-H. Lin, M. M. Ittmann, and E. T. H. Yeh, "SENP1 induces prostatic intraepithelial neoplasia through multiple mechanisms," *Journal of Biological Chemistry*, vol. 285, no. 33, pp. 25859–25866, 2010.

[46] Q. Wang, N. Xia, T. Li et al., "SUMO-specific protease 1 promotes prostate cancer progression and metastasis," *Oncogene*, vol. 32, no. 19, pp. 2493–2498, 2013.

[47] L. I. Pei-Yuan, L. N. Huo, S. U. Wei, L. Y. Deng, M. P. Peng, and Z. X. Zhang, *Radical Scavenging Activity And Total Phenolics Content Of Kochia Scoparia*, Hubei Agricultural Sciences, Wuhan, China, 2016.

[48] J. Wang, L. Hou, H. Zhang, Y. Zhang, and X. F. Chen, *Study On Comparison Of Free Radical Scavenging Activities In The Ethanol Kochia Scoparia Extract*, Journal of Shaanxi University of Science & Technology, Xi'an, China, 2017.

[49] Z. Hao, "Antioxidant activities of flavonoids extraction from Kochia scoparia," *Chemical Industry Times*, 2012.

[50] M. Yan, W. Zhang, G. Luo, X. Wang, S. Feng, and N. Zhao, "Screening chemical constituents with antioxidative activity from the kochiae fructus," *Chinese Medicine Journal of Research & Practice*, vol. 33, no. 4, pp. 29–32, 2019.

[51] H. Jeon, D. H. Kim, Y. H. Nho, J. E. Park, S. N. Kim, and E. H. Choi, "A mixture of extracts of Kochia scoparia and rosa multiflora with PPAR α/γ dual agonistic effects prevents photoaging in hairless mice," *International Journal of Molecular Sciences*, vol. 17, no. 11, 2016.

[52] Y. F. Xia, Q. Wang, X. U. De Ran, H. Wang, and Y. E. Wen Cai, "Determination of the content of momordin Ic in Kochia scoparia by HPLC," *Journal of China Pharmaceutical University*, vol. 33, no. 3, pp. 216–218, 2002.

[53] X. Y. Feng, W. Qiang, and D. Yue, "Changes of saponin content in Kochia scoparia fruit in different collecting times," *Journal of Plant Resources & Environment*, vol. 11, 2002.

[54] Y. F. Xia, W. Qiang, D. Yue, and P. Kai, "Determination of the content of saponin in Kochia scoparia fruits from different producing areas," *China Journal of Chinese Materia Medica*, vol. 27, no. 12, pp. 890–893, 2002.

[55] X. Zuoqi, W. Xiaoke, O. Bo et al., "Simultaneous determination of rutin and quercetin in kochiae fructus by hplc," *China Medical Herald*, vol. 13, no. 21, pp. 146–152, 2016.

[56] Z. Q. Xiao, B. Ouyang, T. Pan, and X. K. Wen, "Study on HPLC fingerprint of kochiae fructus and their cluster analysis," *Guiding Journal of Traditional Chinese Medicine & Pharmacy*, vol. 23, 2017.