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Progress in Studies on Phytochemistry and Biological Activity of *Folium Eriobotryae*

Jian Chen • Wei-lin Li*

Institute of Botany (Nanjing Botanical Garden, Mem. Sun Yet-sen), Jiangsu Province and the Chinese Academy of Sciences, Nanjing 210014, China

Corresponding author: * lwlcnbg@mail.cnbg.net

ABSTRACT

Eriobotrya japonica (Thunb.) Lindl. is widely planted as a fruit tree, specifically in China and Japan, and its dried leaves (*Folium Eriobotryae*) is commonly used in traditional Chinese medicine. Many compounds including essential oil, triterpenes, sesquiterpenes, flavonoids, tannins and megastigmane glycosides have been isolated from *Folium Eriobotryae*, and showed anti-inflammatory, hypoglycemic, anti-oxidant, anti-tumor, antiviral, cytotoxic and antimutagenic properties. In the present paper we review the research results on phytochemical constituents and biological activities of *Folium Eriobotryae* in the hope that it would be helpful to better understand and use traditional Chinese medicine.

Keywords: antidiabetic, anti-inflammatory, antitumor, antioxidant, *Eriobotrya japonica* (Thunb.) Lindl., flavonoids, sesquiterpenes, triterpene

CONTENTS

INTRODUCTION

Eriobotrya japonica (Thunb.) Lindl. (Rosaceae) is widely planted as a fruit tree, specifically in China and Japan, and its dried leaves (*Folium Eriobotryae*, known as "Pipaye") have commonly been used in traditional Chinese medicine prescriptions as an antitussive and anti-inflammatory agent to clear away lung-heat, eliminate phlegm, lower the adverse-rising energy, relieve cough and regulate the stomach to restrain vomiting skin diseases, as well as in Japanese folk medicine (known as "Biwayo") as a diuretic, digestive, and antipyretic agent to treat skin diseases, relieve inflamemation, pain, coughing, and sputa (Namba 1994). To prove these ethno-medical claims, pharmacological research work is being extensively carried out to prove these biological activities using various animal models. Along with biological activity studies, isolation and identification of chemical constituents from *Folium Eriobotryae* and their correlation with biological activities have also been studied.

Many compounds including essential oil, triterpenes, sesquiterpenes, flavonoids, tannins and megastigmane glycosides have been found from *Folium Eriobotryae*, among which, some have been reported to be biologically active, exhibiting anti-inflammatory, hypoglycemic, anti-oxidant, anti-tumor, antiviral, cytotoxic, or antimutagenic properties. In China, the planting area of *E. japonica* exceeds 200,000 acres and farmers collect ~300,000 metric tons per year of deciduous leaves. Besides local consumption in pharmaceutical preparations produce, the extract of *Folium Eriobotryae* is always exported to Japan, Europe and the USA for medical or cosmetic use.

PHYTOCHEMISTRY

Efforts have been made by researchers to isolate and identify biologically active principles and other major chemical constituents from *Folium Eriobotryae*.

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Invited Mini-Review

Table 1 Ursane-type triterpenes isolated from *Folium Eriobotryae*.

Compound	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9
1	H	H	H	H	OH	H	H	H	H
2	H	H	OH	H	OH	H	H	H	H
3	H	H	H	H	OH	H	OH	OH	H
4	H	H	OH	OH	H	H	H	OH	H
5	H	H	H	H	OH	H	H	OH	H
6	H	H	OH	H	OH	H	H	OH	H
7	H	H	H	H	OH	H	H	H	CH_3
8	H	H	OH	OH	H	H	H	H	H
9	OH	H	OH	OH	H	H	H	OH	H
10	H	OH	H	H	OH	H	H	OH	H
11	H	OH	H	OH	H	H	H	H	H
12	H	H	OH	H	OH	*E*-coumaroyl-O-	H	OH	H
13	H	H	OH	H	OH	*Z*-coumaroyl-O-	H	OH	H
14	H	H	OH	H	*E*-caffeoyl-O-	H	H	OH	H
15	H	H	H	OH	*E*-coumaroyl-O-	H	H	OH	H
16	H	H	OH	*E*-feruloyl-O-	H	H	H	H	H

Essential oil

There are many kinds of essential oil in the *Folium Eriobotryae*, such as nerolidol, farnesol, α- pinene, β-pinene, camphene, β-myrcene, *p*-cymene, linalool, *trans*-linalool oxide, α-ylangene, α-farnesene, β-farnesene, camphor, nerol, geraniol, α-cadinol, *cis*-β, γ-hexenol, in which nerolidol accounts for 61~74% (Zheng *et al*. 1998).

Triterpenes

Large amounts of triterpenes have been isolated from *Folium Eriobotryae*. More than 20 triterpene acids, including 16 of the ursane-type (1-16) (**Fig. 1, Table 1**), four of the oleanane-type (17-20) (**Fig. 2, Table 2**), and four other types (21-24) (**Fig. 3**), were isolated and identified from *Folium Eriobotryae*. They are ursolic acid (1), 2α-hydroxyursolic acid (corosolic acid, 2), 3β, 6α, 19α-trihydroxyurs-12-en-28-oic acid (3) (Liang *et al*. 1990), 2α, 3α, 19α-trihydroxyurs-12-en-28-oic acid (euscaphic acid, 4) (Shimizu *et al*. 1986), 3β, 19α-dihydroxyurs-12-en-28-oic acid (pomolic acid, 5) (Ju *et al*. 2003), 2α, 3β, 19α-trihydroxyurs-12-en-28-oic acid (tormetic acid, 6), methyl ursolate (7) (Banno *et al*. 1995), 2α, 3α-dihydroxyurs-12-en-28-oic acid (3-epicorosolic acid, 8), 1β-hydroxyeuscaphic acid (9) (de Tommasi *et al*. 1991), 2β, 3β, 19α-trihydroxyurs-12-en-28-oic acid (10) (Chen *et al*. 2006), 2β, 3α-dihydroxyurs-12-en-28-oic acid (11) (Chen *et al*. 2006), 23-*trans*-*p*- coumaroyltormentic acid (12), 23-*cis*-*p*-coumaroyltormentic acid (13), 3-*O*-*trans*-caffeoyltormentic acid (14), 3-*O*-*trans*-*p*-coumaroylrotundic acid (15), 3-*O*-*trans*-feruloyleuscaphic acid (16) (de Tommasi *et al*. 1992), oleanolic acid (17), 2α-hydroxyoleanolic acid (maslinic acid, 18) (Shimizu *et al*. 1986), methyl arjunolate (19), 2α,3α,23-trihydroxyolean-12-en-28-oic acid (20), usrolic acid lactone (21), betulinic acid (22), δ-oleanolic acid (23) (Banno *et al*. 1995) and hyptadienic acid (24) (Taniguchi *et al*. 2002).

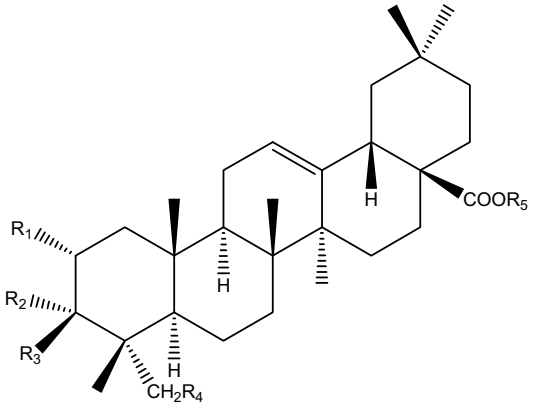


Fig. 2 Oleanane-type triterpene parent nucleus.

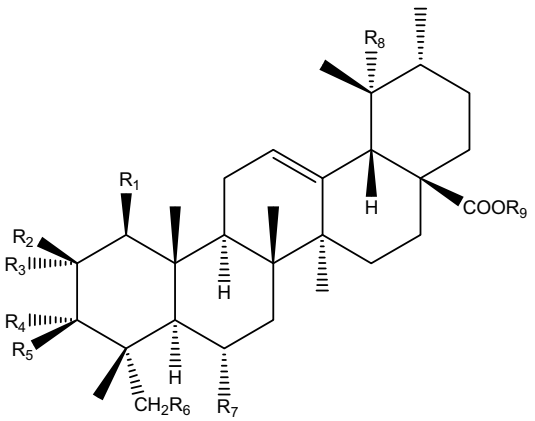


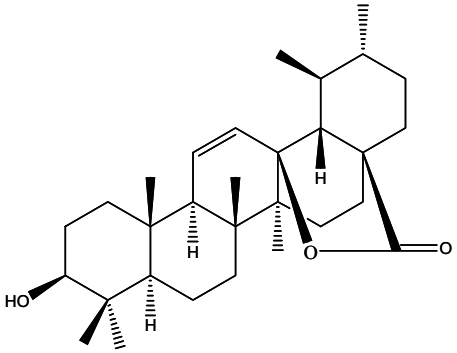
Fig. 1 Ursane-type triterpene parent nucleus.

Table 2 Oleanane-type triterpenes isolated from *Folium Eriobotryae*.

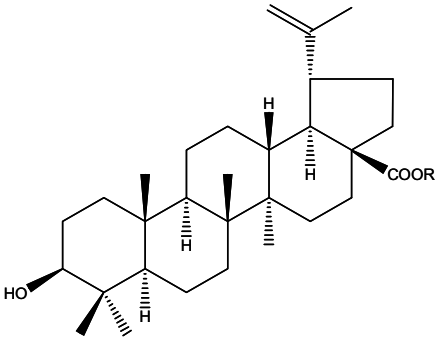
Compound	R_1	R_2	R_3	R_4	R_5
17	H	H	OH	H	H
18	OH	H	OH	H	H
19	OH	H	OH	OH	CH_3
20	OH	OH	H	OH	H

Sesquiterpenes

Many sesquiterpenes were found from *Folium Eriobotryae*, most of them are sesquiterpene glycosides characterized by nerolidol (**Fig. 4, Table 3**) or isohumbertiol (**Fig. 5, Table 4**) as aglycones and by branched oligosaccharidic chains made up of α-L-rhamnopyranosyl and β-D-glucopyranosyl units. They are: nerolidol-3-*O*-[α-L-rhamnopyranosyl (1→4)-α-L-rhamnopyranosyl(1→6)]-β-D-glucopyranoside (25), nerolidol-3-O-α-L-rhamnopyrano-syl(1→2)-β-D-glucopyranoside (26), nerolidol-3-*O*-[α-L-rhamnopyranosyl (1→4)-α-L-rhamnopyranosyl(1→2)]-β-D-glucopyranoside (27), nerolidol-3-*O*-{[α-L-rhamnopyrano-syl(1→4)-α-L-rhamnopyranosyl(1→2)]-α-L-rhamnopyrano-syl(1→6)}-β-D-glucopyranoside (28) (de Tommasi *et al*. 1990), nerolidol-3-*O*-α-L-rhamnopyranosyl(1→2)-[α-L-rhamnopyranosyl(1→6)]-β-D-glucopyranoside (29) (Yanagisawa *et al*. 1988), nerolidol-3-*O*-{[α-L-rhamnopyranosyl (1→4)-α-L-rhamnopyranosyl(1→2)]-α-L-(4-*trans*-feruloyl)-rhamnopyranosyl(1→6)}-β-D-glucopyranoside (30) (de Tommasi *et al*. 1992), Isohumbertiol-3-*O*-{α-L-rhamnopyranosyl-(1→4)-α-L-rhamnopyranosyl-(1→2)-[α-L-rhamnopyranosyl-(1→6)]}-β-D-glucopyranoside (31) and Isohumbertiol-3-*O*-{α-L-rhamnopyranosyl-(1→4)-α-L-rhamnopy-

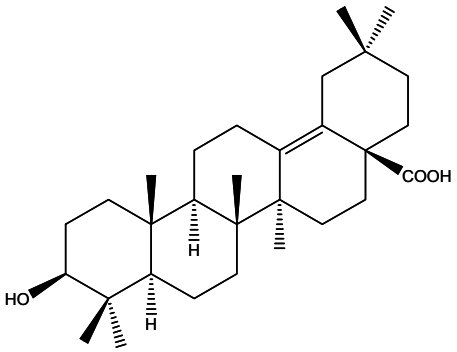


Compound 21

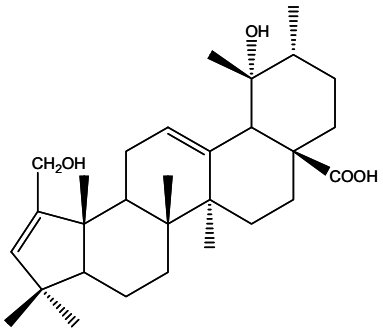


Compound 22

Fig. 3 Other triterpenes isolated from *Folium Eriobotryae*.



Compound 23



Compound 24

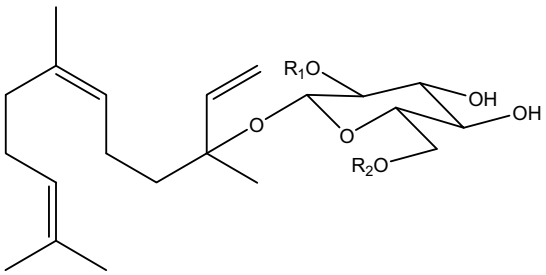


Fig. 4 Open loop-type sesquiterpenoid parent nucleus.

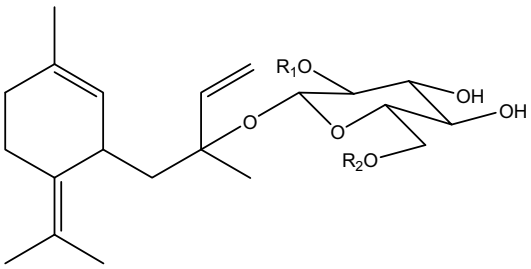


Fig. 5 Closed loop-type sesquiterpenoid parent nucleus.

Table 3 Open loop-type sesquiterpenoids isolated from *Folium Eriobotryae*.

Compound	R_1	R_2
25	H	α-L-Rha (1→4)-α-L-Rha (1→)
26	α-L-Rha (1→)	H
27	α-L-Rha (1→4)-α-L-Rha (1→)	H
28	α-L-Rha (1→4)-α-L-Rha (1→)	α-L-Rha (1→)
29	α-L-Rha (1→)	α-L-Rha (1→)
30	α-L-Rha (1→4)-α-L-Rha (1→)	(4-*trans*-feruloyl)-α-L-Rha (1→)

Table 4 Closed loop-type sesquiterpenoids isolated from *Folium Eriobotryae*.

Compound	R_1	R_2
31	α-L-Rha (1→4)-α-L-Rha (1→)	α-L-Rha (1→)
32	α-L-Rha (1→4)-α-L-Rha (1→)	(4-*trans*-feruloyl)-α-L-Rha (1→)

ranosyl-(1→2)-[α-L-(4-*trans*-feruloyl)-rhamnopyranosyl-(1→6)]}-β-D-glucopyranoside (32) (de Tommasi *et al*. 1992).

Flavonoids

During the chemical investigation of *Folium Eriobotryae*, some flavonol glycosides (**Fig. 6, Table 5**) were also isolated. Here are the typical ones: kaempherol (35) (Hung *et al*. 1999), quercetin (36), quercetin-3-*O*-glucoside (37), quercetin-7-α-L-rhamnoside (38), quercetin-3-*O*-sophoroside (39), hyperoside (40), quercetin-3-*O*-rutinoside (41) (Louati *et al*. 2003), quercetin-3-sambubioside (42) (Jung *et al*. 1999), quercetin-3-rhamnoside (43), kaempherol-3-*O*-

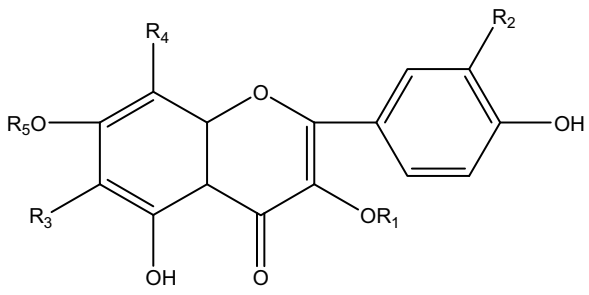


Fig. 6 Flavonoid parent nucleus.

Table 5 Flavonoids compounds isolated from *Folium Eriobotryae*.

Compound	R_1	R_2	R_3	R_4	R_5
35	H	H	H	H	H
36	H	OH	H	H	H
37	β-D-Glc	OH	H	H	H
38	H	OH	H	H	α-L-Rha
39	β-D-Glc (1→2) -β-D-Glc	OH	H	H	H
40	Gala	OH	H	H	H
41	Rutinoside	OH	H	H	H
42	Xyl (1→2) -β-D-Glc	OH	H	H	H
43	α-L-Rha	OH	H	H	H
44	β-D-Glc	H	H	H	H
45	Gala	H	H	H	H
46	α-L-Rha (1→2) -β-D-Glc	H	H	H	H
47	α-L-Rha	H	H	H	H
48	Rutinoside	H	H	H	H
49	β-D-Glc (1→2) -β-D-Glc	H	H	H	H
50	(2″, 4″-di-E-feruloyl)-α-L-Rhamnoside	H	H	H	H
51	(2″, 4″-di-E-coumaruyl)-α-L-Rhamnoside	H	H	H	H
52	(2″, 4″-di-Z-coumaruyl)-α-L-Rhamnoside	H	H	H	H
53	Gala	OCH_3	H	H	H
54	H	H	β-D-Glc	β-D-Glc	H

glucoside (44), kaempherol-3-*O*-galactoside (45), kaempherol-3-*O*-nehesperidoside (46), kaempherol-3-*O*-rhamnoside (47), kaempherol-3-rutinoside (48), kaempherol-3-*O*-sophroside (49) (Louati *et al*. 2003), kaempherol-3-*O*-α-L-(2", 4"-di-E-feruloyl)-rhamnoside (50), kaempherol-3-*O*-α-L-(2", 4"-di-E-P-coumaroyl)-rhamnoside (51), kaempherol-3-*O*-α-L-(2", 4"-di-Z-P-coumaroyl)-rhamnoside (52) (Kawahara *et al*. 2002), isorhamnetin-3-*O*-galactoside (53) and c-glycoside schaftoside (54) (Louati *et al*. 2003).

Other constituents

There are also other chemical constituents isolated from *Folium Eriobotryae*, such as vomifoliol-9-*O*-β-D-glucopyranoside, 3-oxo-α-ionyl-9-*O*-β-D-glucopyranoside, 3-oxo-α-ionyl-9-*O*-β-D-apiofuranosyl-(1→6)-β-D-glucopyranoside and vomifoliol-9-*O*-β-D-apiofuranosyl-(1→6)-β-D-glucopyranoside (de Tommasi *et al*. 1992), Chlorogenic acid, 3-*O*-caffeoylquinic acid, 4-*O*-caffeoylquinic acid, 4-*O*-p-coumaroylquinic acid (Ito *et al*. 2000), amygdalin, tartaric acid, citric acid (Zheng *et al*. 1998), etc.

BIOLOGICAL ACTIVITIES

Folium Eriobotryae is being used in various health care systems for the treatment of various disorders including life-threatening diseases. To validate traditional claims, many studies are being carried out using various animal models and *in vitro* assays. These studies showed that *Folium Eriobotryae* possesses potent anti-inflammatory, antidiabetic, antioxidant and antitumor activities and has the potential to be developed as potent remedial agents from natural resources. Some major activities are described below.

Anti-inflammatory activity

Inflammation is a very complex pathophysiological process involving a variety of biomoleucles responsible for causing it such as leucocytes, macrophages, mast cells, platelets and lymphocytes by releasing eicosanoids and nitric oxide. Pro-inflammatory cytokines such as TNF-α and IL-1β are also responsible for various inflammatory conditions. Much research on the anti-inflammatory activity of *Folium Eriobotryae* showed that triterpene acids are possibly the biologically active principles.

The earliest report about the anti-inflammatory activity of *Folium Eriobotryae* appeared in 1986 (Shimizu *et al*. 1986). It was proved that methylchlorogenic acid is a potent suppressor of BHP-induced NFκB activation based on that a significant reduction by methylchlorogenic acid on BHP-induced translocation of p65 subunit of NFκB was observed. That result suggested that methylchlorogenic acid may inhibit NFκB activation, exhibiting its ability to downregulate the NFκB-dependent gene expression and may have the potential for therapeutic intervention on various NFκB-dependent pathological conditions such as inflammatory or possibly mutagenic processes (Kwon *et al*. 2000). Ursolic acid, maslinic acid, and the total triterpene acids from *Folium Eriobotryae* exhibited strong anti-inflammatory activity in tests of their effects on ear swelling induced by xylene in mice (Ju *et al*. 2003). Twelve triterpene acids were evaluated for their inhibitory effects on 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced inflammation (1 μg/ear) in mice. All the tested compounds showed a marked anti-inflammatory effect, with a 50% inhibitory dose (ID50) of 0.03-0.43 mg per ear (Banno *et al*. 2005).

Antidiabetic activities

In our investigation of traditional Chinese herbs for folk usage, we discovered that *Folium Eriobotryae* was used to treat diabetes in the rural area of Suzhou, Jiangsu province in east China (Li *et al*. 2004). A decoction made from the dried leaves of *Eriobotrya japonica* is used in the local control and management of suspected diabetic patients both in the past and at present. Subsequent studies on the antidiabetic activity of *Folium Eriobotryae* validate the usage through animal tests.

The alcoholic extract of *Folium Eriobotryae* produced a significant hypoglycemic effect when administered orally to normal rabbits, but did not show any significant effect on blood glucose levels to alloxan-treated rabbits (Noreen *et al*. 1988). In Mexico, one result showed that *Folium Eriobotryae* decreased significantly ($p<0.05$) the area under the glucose tolerance curve, in relation with the water control (Roman *et al*. 1991).

Some studies on the chemical constituents from *Folium Eriobotryae* also proved to have anti-hyperglycemic activity. The content of tormentic acid in the callus tissues with antidiabetic action was much larger than that in the intact leaves (Taniguchi *et al*. 2002). The sesquiterpene glycoside (nerolidol-3-*O*-[α-L-rhamnopyranosyl(1→4)-α-L-rhamnopyranosyl (1→6)]-β-D-glucopyranoside) and two polyhydroxylated triterpenoids (corosolic acid and pomolic acid) produced a marked inhibition of glycosuria in genetically diabetic mice (C57BL/KS-db/db/Ola). Furthermore, the two polyhydroxylated triterpenoids were able to reduce blood glucose levels in normoglycemic rats (de Tommasi *et al*. 1991). Our research also showed that the 70% ethanol extract of *Folium Eriobotryae* exerted a significant hypoglycemic effect to al-

loxan-diabetic mice and the total sesquiterpenes had significantly effect on lowering blood glucose level to normal or/and alloxan-diabetic mice (Li *et al*. 2007). The nerolidol-3-*O*-α-L-rhamnopyranosyl(1→4)-α-L-rhamnopyranosyl (1→2)-[α-L-rhamnopyranosyl(1→6)]-β-D-glucopyranoside isolated from *Folium Eriobotryae* in dose of 25 mg/kg significantly decreased in blood glucose from 21.96 ± 5.68 mmol/L to 16.05 ± 5.51 mmol/L at 2 hours and 14.37 ± 6.14 mmol/L (P<0.05) at 4 hours after the oral administration to alloxan-diabetic mice. Moreover, in the high-dose group, the oral administration with the sesquiterpene glycoside 75 mg/kg had more effect to lower the blood glucose level of alloxan-diabetic mice (P<0.01). Respectively, the dosages of 25 mg/kg and 75 mg/kg also showed a slight effect in normal mice (Chen *et al*. 2008). It is considered that the triterpene acids and sesquiterpene glycosides may be effective constituents for lowering blood glucose, and presume that the sesquiterpene glycosides have a similar action mechanism like agents to treat type 1 diabetes mellitus, and triterpene acids have a similar action mechanism like agents to treat type 2 diabetes mellitus.

Antioxidant activities

The methanolic extract and EtOAc and *n*-BuOH soluble fractions of *Folium Eriobotryae* showed strong antioxidant activity by measuring the radical scavenging effect on DPPH (1, 1-diphenyl-2-picrylhydrazyl) radical and lipid peroxidation. Antioxidant flavonoids and chlorogenic acid also showed prominent inhibitory activity against free radical generation in dichlorofluorescein (DCF) method (Jung *et al*. 1999). One study was to evaluate the effect of triterpene acids of *E. japonica* leaf (TAL) on expression of antioxidative mediators by alveolar macrophages in rats with chronic bronchitis. The levels of methylene dianiline (MDA) and heme oxygenase-1 (HO-1)expressed by cultured alveolar macrophages (AM) and the HO-1 activity in the lung of the drug groups were significantly lower than those from the chronic bronchitis (CB) group without treatment (p<0.01 and p<0.05, respectively), while the superoxide dismutase (SOD) levels increased in a dose-dependent manner by TAL treatment. These results suggest that TAL inhibits HO-1 expression and MDA production and up-regulates SOD expression in AM from CB rats, which might be one of molecular mechanisms of its anti-inflammatory effects in CB rats (Huang *et al*. 2006). There was also one significant result on the seed extract of *E. japonica*. In the *n*-BuOH, MeOH and H_2O fractions, radical scavenging activity and inhibitory activity on lipid peroxidation were high. In addition, these fractions contained abundant polyphenols, and the radical scavenging activity increased with the polyphenol content. In the low-polar Hex and EtOAc fractions, the radical scavenging activity was low, but the lipid peroxidetion inhibition activity was high. These fractions contained β-sitosterol, and the inhibitory activity on lipid peroxidation was high. Based on these findings, the antioxidative activity of seed extract of *E. japonica* may be derived from many components involved in a complex mechanism, resulting in high activity (Yokota *et al*. 2006). Another study showed that the immediate antioxidant effect of *E. japonica* could be associated with the action of vitamin A. The protective action of the fruit of *E. japonica* was seen on mature leukocytes and erythrocytes, beneficial effect on blood cells suggest that its extract could be used as an antioxidant agent complementing the administration of chloramphenicol, as a modern-day extension to its traditional use in Chinese medicine (Eraso and Albesa 2007).

Antitumor activities

Roseoside and procyanidin B-2 isolated from the *Folium Eriobotryae* were assessed for antitumor activity *in vivo* in a two-stage carcinogenesis assay on mouse skin. Roseoside significantly delayed carcinogenesis induced by peroxynitrite (initiator) and TPA (promoter), and its potency was comparable to that of a green tea polyphenol, (-)-epigallocatechin 3-*O*-gallate, in the same assay (Ito *et al*. 2002). Cultured cells of leaves of *E. japonica* producing ursane- and oleanane-type triterpenes with antitumor activities were also established (Taniguchi 2005). In addition, an evaluation against the Epstein-Barr virus early antigen (EBV-EA) activation induced by TPA for some compounds from *Folium Eriobotryae*, two polyhydroxylated triterpene acids showed potent inhibitory effects on EBV-EA induction. And euscaphic acid exhibited marked antitumor-promoting activity in an *in vivo* two-stage carcinogenesis test of mouse tumor by using 7, 12- dimethylbenz[a]anthracene (DMBA) as an initiator and TPA as a promoter (Banno *et al*. 2005).

Other biological activities

Other major biological activities reported for *Folium Eriobotryae* are:

Antiviral

3-*O*-*trans*-caffeoyltormentic acid isolated from *Folium Eriobotryae* could significantly reduce rhinovirus infection but was ineffective towards human immunodeficiency virus type 1 (HIV-1) and Sindbis virus replication (de Tommasi *et al*. 1992);

Antimutagenic

Ursolic acid isolated from the EtOAc extract of *Folium Eriobotryae* markedly and significantly decreased the numbers of *Salmonella typhimurium* TA100 revertants per plate, thus showing antimutagenic activity (Young *et al*. 1994);

Tissue factor activity

3-*O*-α-L-rhamnopyranosyl-(1→4)-α-L-rhamnopyranosyl-(1→2)-[α-L-(4-*trans*-feruloyl)-rhamnopyranosyl-(1→6)]-β-D-glucopyranosyl nerolidol and ferulic acid isolated from *Folium Eriobotryae* inhibited 50% of the TF activity at concentrations of 2 and 369 microM/TF units, respectively (Lee *et al*. 2004).

SUMMARY

With thousands of years of medical practice, a great deal of valuable experience has accumulated in the traditional Chinese medical system for health care. Chinese doctors have put forward many prescriptions [mostly Compound Recipes (prescription with over two medicines)] and have applied them to the therapy. Some classical prescriptions and folk secret recipes with outstanding curative effect have been used for hundreds of years, and are still in use today. Some of them have been developed into preparations for therapy following the progress of modern medical and medicinal technology, and resulted in good effects.

Folium Eriobotryae is one member of this traditional Chinese Medicine kingdom and its extensively usage as folk medicine has been confirmed by studies on its chemical constituents and biological activities. Many compounds including triterpenes, sesquiterpenes, flavonoids, tannins and megastigmane glycosides have been isolated from *Folium Eriobotryae*, and showed anti-inflammatory, hypoglycemic, anti-oxidant, anti-tumor, antiviral, cytotoxic and antimutagenic properties.

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