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Chinese Journal of Natural Medicines 2019, 17(8): 0561–0574

Chinese Journal of Natural Medicines

•Review•

Microcos paniculata: a review on its botany, traditional uses, phytochemistry and pharmacology

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Available online 20 Aug., 2019

[ABSTRACT] The shrub *Microcos paniulata* (MPL; Tiliaceae), distributed in south China, south and southeast Asia, yields a phytomedicine used to treat heat stroke, fever, dyspepsia, diarrhea, insect bites and jaundice. Phytochemical investigations on different parts of MPL indicate the presence of flavonoids, alkaloids, triterpenoids and organic acids. The MPL leaves, fruits, barks and roots extracts showed antidiarrheal, antimicrobial and insecticidal, anti-inflammation, hepatoprotective, cardiovascular protective, blood lipids reducing, analgesic, jaundice-relieving and antipyretic activities, etc. The review aims to summary the traditional uses, botany, phytochemistry, pharmacological bioactivity, quality control, toxicology and potential mechanisms of MPL. Additionally, this review will highlight the existing research gaps in knowledge and provide a foundation for further investigations on this plant.

[KEY WORDS] *Microcos paniculata*; Botany; Traditional uses; Phytochemistry; Pharmacology

[CLC Number] Q5, R965, R284 **[Document code]** A **[Article ID]** 2095-6975(2019)08-0561-14

Introduction

Microcos paniculata (MPL), belonging to family Tiliaceae, is a shrub native to southern China, South Asia and Southeast Asia. Microctis Folium (buzhaye in Chinese), the dried leaves of MPL, is traditionally used as folk medicine and herbal tea materials in China [1].

Many phytochemical investigations on MPL have been carried out [2-3], which reveal the presence of bioactive secondary metabolites including flavonoids, alkaloids, triterpenoids and organic acids etc. The leaves of MPL is ethnomedicinally used for the treatment of abdominal pain and diarrhea, sore throat, damp-heat jaundice, fever, heat stroke, and is often served as general tonics and insecticides in traditional Chinese medicine (TCM) [4]. Pharmacological studies [5-8] have been developed on antidiarrheal, antimicrobial, insecticidal, anti- inflammatory, cardiovascular, liver protecting, blood lipids reducing, analgesic and jaundice-relieving activities of leaves, fruits, barks and roots extracts of MPL.

In the current review, we aim at summarizing the traditional uses, botany, phytochemicals, pharmacological activities, quality control and toxicology of MPL leaves, fruits, barks and roots extracts reported over the past decades. These up-to-date research observations will be helpful in understanding the biological activities of this medicinal plant, as well as applicable in developing new herbal products and functional foods in the future.

Materials and Methods

A literature review of phytochemistry and biological activities of MPL leaves, fruits, barks and roots extracts was performed using published articles in peer-reviewed journals, conference papers, theses, and scientific databases such as PubMed, ScienceDirect and China National Knowledge Infrastructure (CNKI). Ethnobotanical textbooks and internet sources such as www.medicinalplants.in, www.mpbd.info and www.theplantlist.org were used to verify the traditional uses and botany of MPL. The key words "*Microcos paniculata*", "phytochemistry", "pharmacology", "traditional uses", "quality control" and "toxicity" were used to search literature sources.

Traditional Uses

Traditionally, MPL leaves, fruits, barks and roots extracts were used for medicinal purpose by ethnic groups [1, 9-12].

[Received on] 18-Apr.-2019

[Research funding] This work was supportted from the National Natural Science Foundation of China (No. 81673569), National Key Research and Development Program of China (No. 2017YFC1701105) and the Project Funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions.

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These authors have no conflict of interest to declare.

Microctis Folium, distributed in Guangdong, Guangxi, Hainan and Yunnan province of China, was a traditional herbal medicine recorded in the Chinese Pharmacopoeia. In TCM theory, Microctis Folium tastes slightly acid and cool, neutralizes in nature without toxicity and attributes to the spleen and stomach meridians with the bioactivities of relieving dyspepsia, clearing heat and draining dampness [4]. It could be used to alleviate diarrhea, resolve "food stagnation", remove "dampness and jaundice", clear heat and detoxify according to "Standards of Chinese herbal medicines in Guangdong" in China [13]. Microctis Folium was widely recognized as one of the major ingredients in Cantonese herbal tea in China [14]. It was first recorded as a tea drink in the classical herbal text "Shengcaoyaoxing Beiyao" in Qing Dynasty [9]. Besides, the decoction of Microctis Folium at a dose of 15−30 g could be used for treating centipede-bite [1].

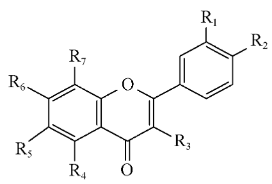
Apart from China, the traditional application of MPL leaves, fruits, barks and roots was also reported in Southeast Asian countries such as Bangladesh, Sri Lanka, India, Indonesia, Myanmar, Malaysia, Andaman Islands, Vietnam, Cambodia and Thailand [10-11]. In these countries, the plant was traditionally used for treatment of indigestion, eczema, itch, small-pox, typhoid fever, wounds, hepatitis, heat stroke, dysentery and syphilitic ulceration of the mouth (http: //www.mpbd.info). Boiled MPL leaves along with turmeric and shell of snail were also used for treatment of jaundice [12].

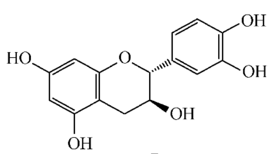
Botany

MPL [Synonym: *Microcos nervosa* (Lour.) S. Y. Hu, *Grewia nervosa* (Lour.) Panigrahi, *Grewia microcos* L. *Fallopia nervosa* Loureiro (http: //www.tropicos.org); belongs to genus *Microcos*, family Tiliaceae, order Malvales and class Dicotyledoneae [15]] is known as Microcos (transcribed English), Kaphla (transcribed Thai), Patka (transcribed Bengali), Shiral (transcribed Hindi) and buzhaye (transcribed Chinese). It is also known as "pobuye", "huobuma", "bengbuye", "paobubu" and "shanzhaye" in folk China [1], and "Kathgua or Fattashi" in local Bangladesh (http: //www.medicinalplants.in; http: //www.mpbd.info). The genus *Microcos* comprises of 60 species in the world and is native to India, Andaman and Nicobar (Andaman Islands), Sri Lanka, China, Cambodia, Myanmar, Thailand, Vietnam, Indonesia and Malaysia (http: //www.theplantlist.org). In China, there are three species of genus *Microcos* including MPL, *Microcos chungii* (Merr.) Chun and *Microcos stauntoniana* G. Don. MPL is a small tree growing about 3−12 m with thin oval-shaped or oblong leathery leaves, rough bark and round or oval drupe [15]. It is a common wild plant which is less cultivated and grown in valley and plain. The leaves of MPL are usually collected in autumn and winter. After removing the branches, it is placed in the shade or in the sun to dry before use [4]. The fresh roots, fruits and barks of MPL are harvested in January and November [5-8, 16-17].

Phytochemistry

To date, a total of 70 compounds have been isolated and identified from leaves, fruits, barks and roots extracts of MPL [2-3, 18-19], including 30 flavonoids, 11 alkaloids, 10 triterpenoids, 9 organic acids, 3 steroids and 7 other compounds. These compounds are documented and listed in Fig. 1 and their structures are displayed in Table 1.





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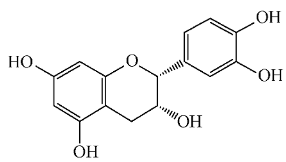

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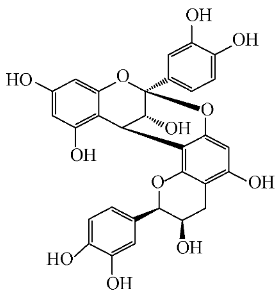
	R1	R2	R3	R4	R5	R6	R7
1	H	OH	H	OH	H	OH	H
2	H	OCH_3	H	OCH_3	OCH_3	OCH_3	OCH_3
3	OCH_3	OCH_3	H	OCH_3	OCH_3	OCH	OCH_3
4	OCH_3	OH	OH	OH	H	OH	H
5	H	OH	OH	OH	H	OH	H
6	O	OH	OH	OH	H	OH	H
10	OCH_3	OH	H	OH	OH	*O*-rutinose	H
11	H	OH	H	OH	OH	*O*-rha	OH
12	H	OH	*O*-*β*-D-glc	OH	H	OH	H
13	H	OH	*O*-3,6-di-*p*-(hydroxycinnamoyl)-glc	OH	H	OH	H
14	OCH_3	OH	*O*-*β*-D-glc	OH	H	OH	H
15	OCH_3	OH	*O*-rutinose	OH	H	OH	H
16	H	OH	*O*-*β*-D-(6-*O*-*trans*-*p*-coumaroyl)-glc	OH	H	OH	H
18	H	OH	*O*-rutinose	OH	H	OH	H
19	H	OH	OH	OH	*O*-D-glc	H	H
20	H	OH	OH	OH	H	*O*-D-glc	H

21	OH	OH	*O*-rutinose	OH	H	OH	H
22	H	H	OH	OH	H	*O*-rutinose	H
23	H	OH	H	OH	H	OH	*β*-D-glc
24	H	OH	H	OH	*β*-D-glc	OH	H
25	H	OH	H	OH	O-glc	OH	L-rha
26	H	OH	H	OH	L-rha	OH	D-glc
28	H	OH	H	OH	D-glc	OH	D-glc
29	OH	OH	H	OH	D-glc	OH	D-xyl



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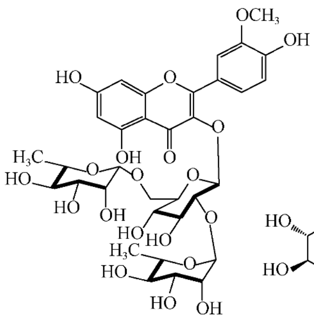

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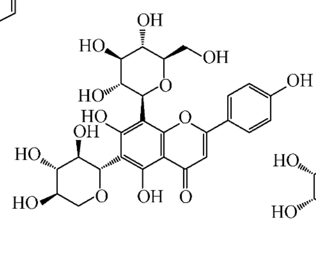

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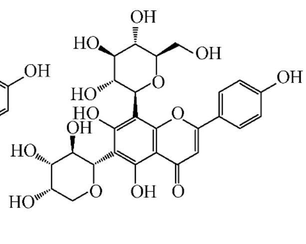

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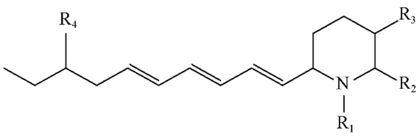
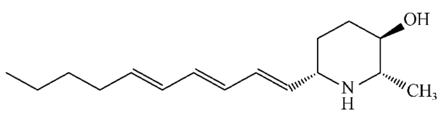


	R_1	R_2	R_3	R_4
32	H	CH_3	OCH_3	H
33	CH_3	CH_3	CH_3	H
34	CH_3	CH_3	H	H



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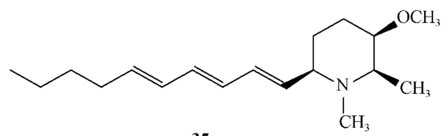

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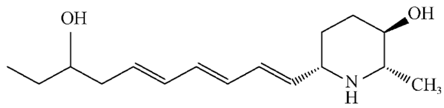

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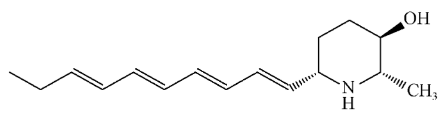

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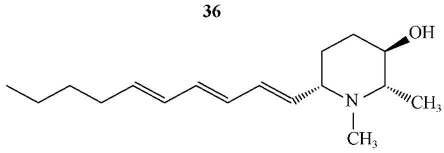

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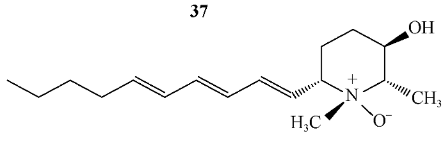

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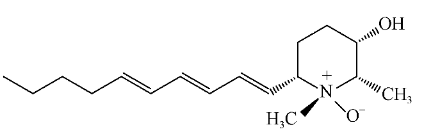

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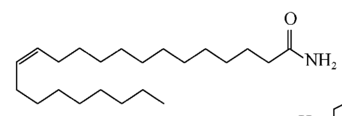

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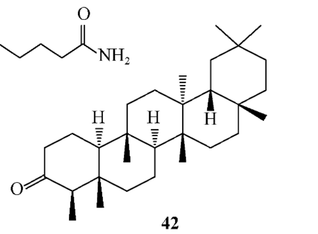

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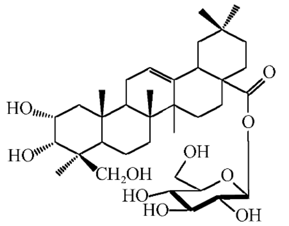

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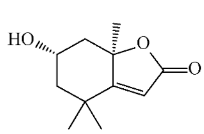

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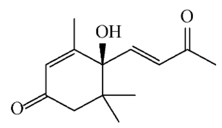

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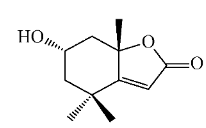

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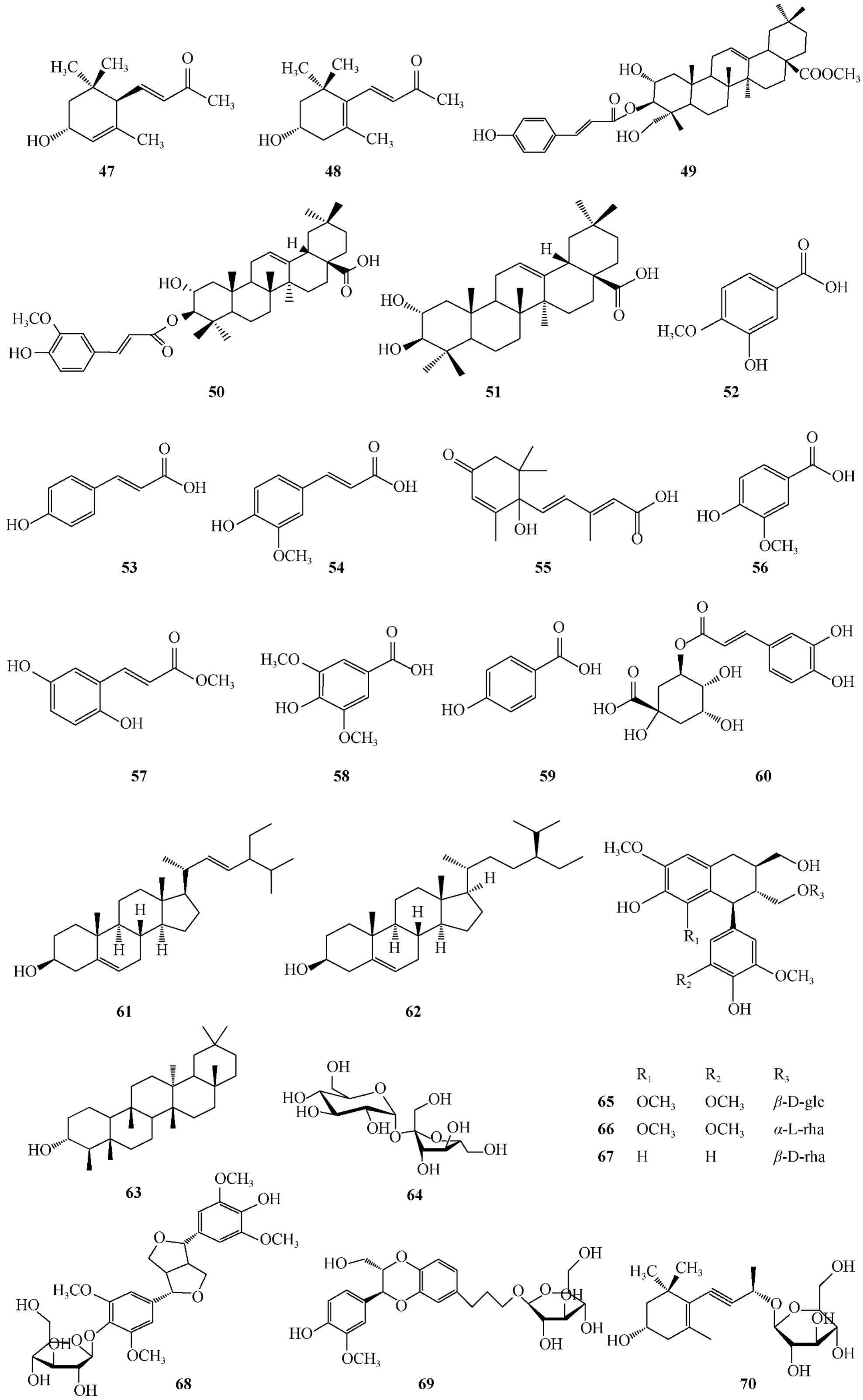

Fig. 1 Chemical structures of the compounds isolated from *Microcos paniculata* (MPL)

Table 1 The compounds identified from *Microcos paniculata* (MPL)

No.	Chemical type	Chemical name	Molecular formula	References
	Flavones	Apigenin	$C_{15}H_{10}O_5$	[2]
		5, 6, 7, 8, 4′-Pentamethoxyflavone	$C_{20}H_{20}O_7$	[21]
		Nobiletin	$C_{21}H_{22}O_8$	[21]
		Isorhamnetin	$C_{16}H_{12}O_7$	[22]
		Kaempferol	$C_{15}H_{10}O_6$	[22]
		Quercetin	$C_{15}H_{10}O_7$	[22]
		Catechin	$C_{15}H_{14}O_6$	[2]
		Epicatechin	$C_{15}H_{14}O_6$	[2]
		Proanthocyanidin A_2	$C_{30}H_{24}O_{12}$	[23]
	Flavonoids glycosides	Nodifloretin-7-*O*-rhamnosyiglucoside	$C_{28}H_{32}O_{16}$	[22]
		5, 6, 8, 4′-Tetrahydroxylflavone-7-*O*-rhamnoside	$C_{21}H_{20}O_{11}$	[22]
		Kaempferol-3-*O*-*β*-D-glucopyranoside	$C_{21}H_{20}O_{11}$	[25]
		Kaempferol-3-*O*-*β*-D-[3, 6-di-*p*-(hydroxycinnamoyl)]-glucopyranoside	$C_{39}H_{32}O_{15}$	[25]
		Isorhamnetin-3-*O*-*β*-D-glucopyranoside	$C_{22}H_{22}O_{12}$	[25]
		Narcissin	$C_{28}H_{32}O_{16}$	[3]
		Kaempferol-3-*O*-*β*-D-(6-*O*-*trans*-*p*-coumaroyl)-glucopyranoside	$C_{30}H_{26}O_{13}$	[2]
		Typhaneoside	$C_{34}H_{42}O_{20}$	[3]
		Kaemferol-3-*O*-rutinoside	$C_{27}H_{30}O_{15}$	[24]
		Kaemferol-6-*O*-glucoside	$C_{21}H_{20}O_{11}$	[24]
		Kaemferol-7-*O*-glucoside	$C_{21}H_{20}O_{11}$	[23]
		Quercetin-3-*O*-rutinoside	$C_{27}H_{30}O_{16}$	[23]
		Apigenin-7-*O*-rutinoside	$C_{27}H_{30}O_{14}$	[23]
		Vitexin	$C_{21}H_{20}O_{10}$	[25]
		Isovitexin	$C_{21}H_{20}O_{10}$	[25]
		Violanthin	$C_{27}H_{30}O_{14}$	[25]
		Isoviolanthin	$C_{27}H_{30}O_{14}$	[25]
		Vicenin-1	$C_{26}H_{28}O_{14}$	[26]
		Vicenin-2	$C_{27}H_{30}O_{15}$	[26]
		Schaftoside	$C_{26}H_{28}O_{14}$	[26]
		Isoschaftoside	$C_{26}H_{28}O_{14}$	[26]
	Alkaloids	*N*-Methyl-6*β*-(deca-l′, 3′, 5′-trienyl)-3*β*-methoxy-2*β*-methylpiperidine	$C_{18}H_{31}NO$	[43]
		6-(Meca-l′, 3′, 5′-trienyl)-3-methoxy-2-methylpiperidine	$C_{17}H_{29}NO$	[28]
		N-Methyl-6-(deca-l′, 3′, 5′-trienyl)-2, 3-dimethylpiperidine	$C_{18}H_{31}N$	[28]
		N-Methyl-6-(deca-l′, 3′, 5′-trienyl)-2-methylpiperidine	$C_{17}H_{29}N$	[28]
		Microcosamine A	$C_{16}H_{27}NO$	[27]
		Microcosamine B	$C_{16}H_{27}NO_2$	[27]
		Microcosamine C	$C_{17}H_{27}NO$	[30]
		Microgrewiapine A	$C_{17}H_{29}NO$	[29]
		Microgrewiapine B	$C_{17}H_{29}NO_2$	[29]
		Microgrewiapine C	$C_{17}H_{29}NO_2$	[29]
		Erucicamide	$C_{22}H_{43}NO$	[21]
	Terpenoids	Friedelin	$C_{30}H_{50}O$	[25]
		Arjunglucoside II	$C_{36}H_{58}O_{10}$	[25]
		Loliolide	$C_{11}H_{16}O_3$	[18]

Continued

No.	Chemical type	Chemical name	Molecular formula	References
	Terpenoids	(+)-Dehydrovomifoliol	$C_{13}H_{18}O_3$	[18]
		Isololiolide	$C_{11}H_{16}O_3$	[3]
		3*R*, 6*R*-3-Hydroxy-*α*-ionone	$C_{13}H_{20}O_2$	[3]
		R-3-Hydroxy-*β*-ionone	$C_{13}H_{20}O_2$	[3]
		3*β*-*O*-*p*-Hydroxy-*E*-cinnamoyloxy-2*α*, 23-dihydroxyolean-12-en-28-oate	$C_{40}H_{56}O_7$	[31]
		3-*trans*-Feruloylmaslinic acid	$C_{40}H_{56}O_7$	[31]
		Maslinic acid	$C_{30}H_{48}O_4$	[31]
	Organic acids	Isovanillic acid	$C_8H_8O_4$	[2]
		p-Coumaric acid	$C_9H_8O_3$	[2]
		Ferulicacid	$C_{10}H_{10}O_4$	[2]
		Abscisic acid	$C_{15}H_{20}O_4$	[2]
		Vanillic acid	$C_8H_8O_4$	[18]
		Syringic acid	$C_9H_{10}O_5$	[18]
		Methyl caffeate	$C_{10}H_{10}O_4$	[18]
		p-Hydroxybenzoic acid	$C_7H_6O_3$	[18]
		Chlorogenic acid	$C_{16}H_{18}O_9$	[32]
	Steroids	Stigmasterol	$C_{29}H_{48}O$	[18]
		β-Sitosterol	$C_{29}H_{50}O$	[18]
		Friedelinol	$C_{30}H_{52}O$	[18]
	Others	Sucrose	$C_{12}H_{22}O_{11}$	[31]
		(+)-Lyoniresinol-2*α*-*O*-*β*-D-glucopyranoside	$C_{28}H_{36}O_{13}$	[23]
		(+)-Lyoniresinol-2*α*-*O*-*α*-L-rhamnopyranside	$C_{28}H_{36}O_{12}$	[23]
		Aviculin	$C_{26}H_{34}O_{10}$	[23]
		(+)-Syringaresinol-4'-*O*-*β*-D-glucoside	$C_{28}H_{36}O_{13}$	[23]
		Junipercomnoside	$C_{25}H_{32}O_{11}$	[23]
		3-Hydroxy-7, 8-didehydro-*β*-ionol-9-*O*-*β*-D-glucopyranoside	$C_{19}H_{32}O_7$	[23]

Flavonoids

Flavonoids were the most abundant components of MPL leaves and the content of flavonoids in leaves, stems, fruits of MPL were 16.94%, 5.15% and 1.52%, respectively [20].

Flavones

Flavones in MPL leaves could be divided into flavones including apigenin (**1**), 5, 6, 7, 8, 4′-pentamethoxyflavone (**2**) and nobiletin (**3**) [2, 21], flavonols including isorhamnetin (**4**), kaempferol (**5**) and quercetin (**6**) [22], along with flavan-3-ols including catechin (**7**) and epicatechin (**8**) [2]. Additionally, proanthocyanidin A_2 (**9**) was identified by liquid chromatograph-mass spectrometry (LC-MS) [23].

Flavonoids glycosides

Flavonoid glycosides in MPL leaves could be classified as flavone *O*-glycosides and flavone *C*-glycosides. The flavone *O*-glycosides included nodifloretin-7-*O*-rhamnosyiglucoside (**10**), 5, 6, 8, 4′-tetrahydroxylflavone-7-*O*-rhamnoside (**11**), kaempferol-3-*O*-*β*-D-glucopyranoside (**12**), kaempferol-3-*O*-*β*-D-[3, 6-di-*p*(hydroxycinnamoyl)]-glucopyranoside (**13**), isorhamnetin-3-*O*-*β*-D-glucopyranoside (**14**), narcissin (**15**), kaempferol-3-*O*-*β*-D-(6-*O*-*trans*-*p*-coumaroyl)-glucopyranoside (**16**), typhaneoside (**17**), kaemferol-3-*O*-rutinoside (**18**) and kaemferol-6-*O*-glucoside (**19**) [3, 22, 24-25]. Besides, kaemferol-7-*O*-glucoside (**20**), quercetin-3-*O*-rutinoside (**21**) and apigenin-7-*O*-rutinoside (**22**) were identified by high performance liquid chromatography (HPLC) [23]. The flavone *C*-glycosides included vitexin (**23**), isovitexin (**24**), violanthin (**25**), isoviolanthin (**26**), vicenin-1 (**27**), vicenin-2 (**28**), schaftoside (**29**) and isoschaftoside (**30**) [23, 25-26].

Alkaloids

The alkaloids in MPL barks and leaves included N-methyl-6*α*-(deca-l′, 3′, 5′-trienyl)-3*β*-methoxy-2*β*-methylpiperidine (**31**) isolated from the MPL stem barks [19] as well as 6-(deca-l′, 3′, 5′-trienyl)-3-methoxy-2-methylpiperidine (**32**), *N*-methyl-6-(deca-l′, 3′, 5′-trienyl)-2, 3-dimethylpiperidine (**33**), *N*-methyl-6-(deca-l′, 3′, 5′-trienyl)- 2-methylpiperidine (**34**), micrococsamine A (**35**), micrococsamine B (**36**), micrococsamine C (**37**) microgrewiapine A (**38**), microgrewiapine B (**39**), microgrewiapine C (**40**) and erucicamide (**41**) isolated from MPL leaves [21, 27-30].

Terpenoids

The friedelin (**42**), arjunglucoside II (**43**) were isolated from leaves chloroform extract [25]; loliolide (**44**), (+)-dehydrovomifoliol (**45**) were isolated from leaves ethyl acetate and *n*-butanol extracts [18]; isololiolide (**46**), 3*R*, 6*R*-3-hydroxy-*α*-ionone (**47**), *R*-3-hydroxy-*β*-ionone (**48**) were isolated from leaves ethyl acetate extract [3];

3*β*-*O*-*p*-hydroxy-*E*-cinnamoyloxy-2*α*, 23-dihydroxyolean-12-en-28-oate (**49**), 3-*trans*-feruloylmaslinic acid (**50**) and maslinic acid (**51**) were isolated from stems ethyl acetate extract [31].

Organic acids

The organic acids isolated from MPL leaves included isovanillic acid (**52**), *p*-coumaric acid (**53**), ferulicacid (**54**), abscisic acid (**55**), vanillic acid (**56**), syringic acid (**57**), methyl caffeate (**58**), *p*-hydroxybenzoic acid (**59**) and chlorogenic acid (**60**) [2, 18, 32].

Steroids

The stigmasterol (**61**), *β*-sitosterol (**62**) and friedelinol (**63**) were isolated and identified from MPL leaves [18].

Others

MPL leaves also contained saccharides such as sucrose (**64**) and volatile oils whose main components were hydrocarbons and fatty acids [31, 33]. Besides, five lignan glycosides including (+)-lyoniresinol-2*α*-*O*-*β*-D-glucopyranoside (**65**), (+)- lyoniresinol-2*α*-*O*-*α*-L-rhamnopyranside (**66**), aviculin (**67**), (+)-syringaresinol-4′-*O*-*β*-D-glucoside (**68**), junipercomnoside (**69**) and one megastigmadien glycoside called 3-hydroxy-7, 8-didehydro-*β*-ionol-9-*O*-*β*-D-glucopyranoside **70** were identified from MPL leaves by LC-MS [18, 23].

Quality control

Quality control is very important for bioactivities, safety, and batch-to-batch uniformity of MPL leaves. The quality assessment of MPL mainly focused on the analysis of certain flavonoids in its leaves [34]. According to Chinese Pharmacopoeia, vitexin (**23**) was selected as the quality control marker of Microctis Folium and the content of vitexin (**23**) is required to be more than 0.040% of the dried leaves by HPLC analysis [4]. TAN [35] determined the content of flavonoids in Microctis Folium by ultraviolet spectrophotometry using rutin as reference substance, however, the method was not accurate enough to quantify the flavonoids in Microctis Folium. CHEN *et al.* [36] determined ferulic acid, vitexin (**23**), isovitexin (**24**), kaempferol-3-*O*-*β*-D-rutinoside and narcissoside in Microctis Folium by HPLC. The DNA molecular identification could provide a quick and accurate way to identify species. TANG *et al.* [37] reported the identification of Microctis Folium adulterants *Microcos chungii* (Merr.) Chun and *Mallotus Furetianus* using ITS2 sequence as a barcode. By using high throughput transcriptome sequencing, LIN [38] obtained the transcriptome data of Microctis Folium from four different developmental stages, and excavated candidate genes and regulatory factors in apigenin *C*-glycosides biosynthesis pathway. That study might lay a foundation for germplasm conservation of Microctis Folium. Presently, the quality traits and quality evaluation of Microctis Folium have not been studied deeply, in the future, researchers should further investigate the bioactive constituents of Microctis Folium and establish the quality control standard accordingly.

Biological activities

Biological activities and chemical compounds of MPL are summarized in Table 2 and are discussed in detail below.

Gastrointestinal activity

Digestion promoting activity

DAI *et al.* [39] reported the digestion promoting activity of MPL leaves in rats for 7 days. The *n*-butanol, ethyl acetate and water extracts of MPL leaves (16.8 $g \cdot kg^{-1}$) showed a significant activity in promoting digestion, and their main mechanism was to diminish gastric juice pH and increase the amount of gastric juice and pepsin. With xiangsha yangwei pills (a TCM preparation for treating dyspepsia, 3 $g \cdot kg^{-1}$) as positive control, the water extract was conducted on intestinal ink propulsion test in mice. Though different groups (5.85, 11.7 and 23.4 $g \cdot kg^{-1}$) had no significant effect compared with the normal group, the high and medium dose groups showed an promoting trend in ink propulsion rate, suggesting that these groups may promote gastrointestinal motility mildly [40]. However, the minimum effective dose of water extract (5.85 $g \cdot kg^{-1}$) used was too high, as compared with the traditional dosage of MPL leaves of 15−30 $g \cdot d^{-1}$ for human [2]. Likewise, only single-dose (16.8 $g \cdot kg^{-1}$) was used for *n*-butanol and ethyl acetate extracts in that study.

Antidiarrheal activity

Aziz *et al.* [41] investigated the antidiarrheal activity of MPL fruits. The results indicated the chloroform extract of MPL fruits produced antidiarrheal activity in case of both of castor oil or $MgSO_4$ induced diarrheal models. The inhibition of defecation at 200 and 400 $mg \cdot kg^{-1}$ (i. g.) of MPL fruits reached to 77.78% and 83.33%, respectively for castor oil induced diarrheal mode in mice. While in $MgSO_4$ induced diarrheal model, the inhibition of defecation at 200 and 400 $mg \cdot kg^{-1}$ (i.g.) was 80.65% and 90.32%, respectively. In another study, Moushome *et al.* [8] evaluated the antidiarrheal activity of hydromethanol and petroleum benzene extract of MPL barks. In case of castor oil induced diarrheal test, hydromethanol extract and petroleum benzene extract at 200 and 400 $mg \cdot kg^{-1}$ produced antidiarrheal activity in mice. The highest and significant percentage of inhibition of diarrhea (62.95%) was revealed by hydromethanol extract of MPL barks at 400 $mg \cdot kg^{-1}$. In case of MgSO4 induced diarrheal test, all of the extracts at doses of 200 and 400 $mg \cdot kg^{-1}$ also significantly decreased the total number of diarrheal feces. The Highest and most significant percentage of inhibition of diarrhea (68.13%) were revealed by petroleum benzene extract of MPL barks at 400 $mg \cdot kg^{-1}$. However, the highest does tested of MPL bark extracts was still less effective than the positive control loperamide HCL in both diarrheal models. Rahman *et al.* [42] also found that methanol extract of MPL leaves (200 and 400 $mg \cdot kg^{-1}$, i.p.) could significantly alleviate diarrhea and enteropooling in mice. The extract also reduced gastrointestinal motility in charcoal meal test with the inhibition rate reaching to 20.34% at 200 $mg \cdot kg^{-1}$ and 29.49% at 400 $mg \cdot kg^{-1}$ (i.p.), respectively, while the inhibition rate of loperamide HCL (5 $mg \cdot kg^{-1}$, i.p.) was 40.52%. However, these extracts of MPL were extracted by organic solvents, which were different from the traditional decoction.

Table 2 The pharmacological activities of *Microcos paniculata* (MPL) extracts

Bioactive activity	Plant parts	Fraction or compounds	Assay and route of administration	Results	Ref.
Digestive promoting	Leaves	*n*-Butanol and water extracts (16.8 g·kg^{-1}) *n*-Butanol, ethyl acetate and water extracts (16.8 g·kg^{-1}) *n*-Butanol and water extract (16.8 g·kg^{-1})	Rats (i.g.)	Increase the amount of gastric juice Diminish the gastric juice pH level Increase the pepsin level	[39]
	Leaves	Water extract (5.85, 11.7, 23.4 g·kg^{-1})	Ink propulsion test (i.g.)	Promote the gastrointestinal motility of mice mildly	[40]
Antidiarrheal activity	Fruits	Chloroform extract (200 and 400 mg·kg^{-1})	Castor oil induced diarrhea (i.g.) $MgSO_4$-induced diarrhea (i.g.)	Inhibition rates: 77.78% and 83.33% Inhibition rates: 80.65% and 90.32%	[41]
	Barks	Hydromethanol extract (200 and 400 mg·kg^{-1}) Petroleum benzene extract (200 and 400 mg·kg^{-1})	Castor oil induced diarrhea (i.g.) $MgSO_4$-induced diarrhea (i.g.) Castor oil induced diarrhea (i.g.) $MgSO_4$-induced diarrhea (i.g.) Castor oil induced diarrheal (i.p.)	Inhibition rates: 40.65% ± 3.82% and 62.95% ± 3.23% Inhibition rates: 52.98% ± 4.96% and 63.69% ± 3.35% Inhibition rates: 13.68% ± 4.65% and 38.24% ± 4.39% Inhibition rates: 53.61% ± 3.35% and 68.13% ± 6.13% Inhibition rate: 50.04% (400 mg·kg^{-1})	[8]
	Leaves	Methanol extract (200 and 400 mg·kg^{-1})	Castor oil induced enteropooling (i.p.) Charcoal meal test (i.p.)	Inhibition rates: 25.56% and 39.77 % Inhibition rates: 20.34% and 29.49%, respectively	[42]
Antimicrobial and insecticidal activity	Barks Roots Fruits	Methanol extract (2, 4 and 6 mg/disc) Chloroform extract (2, 4 and 6 mg/disc) Methanol extract (2, 4 and 6 mg/disc)	Agar disc diffusion test (*in vitro*)	*Escherichia coli* and *Serratia spp.* being the most (zone of inhibition 32 mm in both cases at 6 mg/disc) Vibrio cholerae being the most (zone of inhibition 27mm at 6 mg/disc) Proteus mirabilis being the most (zone of inhibition 28 mm at 6 mg/disc)	[6, 16] [17]
	Barks Fruits Roots	Methanol extract Chloroform extract Methanol extract Chloroform extract Methanol extract Chloroform extract	4th Instar larvae of *Culex quinquefasciatus* (*in vitro*)	LC_{50} 299.2 μg·mL^{-1} LC_{50} 360.2 μg·mL^{-1} LC_{50} 342.1 μg·mL^{-1} LC_{50} 441.7 μg·mL^{-1} LC_{50} 257.3 μg·mL^{-1} LC_{50} 267.6 μg·mL^{-1}	[6, 16-17]
	Leaves	Micrococsamine A (**35**) Micrococsamine B (**36**)		LC_{50} 5.2 mg·mL^{-1} LC_{50} 17.0 mg·mL^{-1}	[27]
	Stem barks	*N*-methyl-6*α*-(deca-l′, 3′,5′-trieny)-3*β*-methoxy-2*β*-methylpiperidine (**31**)	2th Instar larvae of the mosquito *Aedes aegypti* (*in vitro*)	LC_{50} 2.1 ppm	[19]
	Fruits	Chloroform extract (50 mg·mL^{-1}) Aqueous extract (50 mg·mL^{-1})	Pheretima posthuma model (*in vitro*)	Cause paralysis at 15.70 min and death at 25.73 min Cause paralysis at 34.24 min and death at 55.25 min	[7, 41]

Continued

Bioactive activity	Plant parts	Fraction or compounds	Assay and route of administration	Results	Ref.
Anti-inflammatory activity	Fruits	Aqueous extract (50−250 μg·mL^{-1})			[5, 7]
	Barks	Methanol extract (200 and 400 mg·kg^{-1})	Trypsin proteinase inhibitory assay (*in vitro*)	IC_{50} 285.47 μg·mL^{-1}	
			Trypsin proteinase inhibitory assay (*in vitro*)	IC_{50} 63.31 μg·mL^{-1}	
			Xylene-induced ear edema test (orally)	Inhibition rates: 19.34% and 36.97%, respectively	
			Cotton pellet-induced granuloma formation (orally)	Inhibition rates: 30.78% and 45.96%, respectively	
	Fruits	Methanol extract (200 and 400 mg·kg^{-1})	Trypsin proteinase inhibitory assay (orally)	IC_{50} 201.55 μg·mL^{-1}	
			Xylene-induced ear edema test (orally)	Inhibition rates: 22.73% and 35.59%, respectively	
			Cotton pellet-induced granuloma formation (orally)	Inhibition rates: 29.76% and 41.86%, respectively	
	Leaves	Apigenin *C*-glycosides (10, 20 and 40 mg·kg^{-1})	LPS-induced ALI model in mice (orally)	Modulating TLR4/TRPC6, reducing the release of pro-inflammatory cytokines, and regulating the expression of apoptosis-related factors	[43]
Analgesic activity	Barks Fruits	Methanol extract (200 and 400 mg·kg^{-1}) Methanol extract (200 and 400 mg·kg^{-1})	Mice paw licking induced by formalin (orally)	Inhibition rates: 25.50%, 42.39%, 43.78% and 53.82%, respectively	[5, 8, 44]
	Barks	Methanol extract (200 and 400 mg·kg^{-1})	Acetic acid-induced writhing in mice (orally)	Inhibition rates: 25.50% ± 4.59%, 42.39% ± 2.45%, 43.78% ± 3.11%, 53.8% ± 3.47%, 52.75% ± 1.95%, 73.98% ± 1.24%, 43.94% ± 1.72%, 63.13% ± 2.51%, 44.10%, 70.77%, respectively	
	Fruits				
	Barks	Methanol extract (200 and 400 mg·kg^{-1}) Hydro-methanol extract (200 and 400 mg·kg^{-1})			
	Leaves	Petroleum benzene extracts (200 and 400 mg·kg^{-1})			
	Barks	Ethanol extract (250 and 500 mg·kg^{-1}) Petroleum benzene extracts (200 and 400 mg·kg^{-1})	Tail immersion test (orally)	Significant increase in latency time at 30 min	
	Fruits	Methanol extract (400 mg·kg^{-1})		Significant increase in latency time at 60 min	
	Barks	Methanol extract (200 and 400 mg·kg^{-1}) Hydro-methanol extracts (200 mg·kg^{-1}) Petroleum benzene extracts (200 mg·kg^{-1})	Hot plate test (orally)	Significant increase in response latency at 30 min	

Continued

Bioactive activity	Plant parts	Fraction or compounds	Assay and route of administration	Results	Ref.
Hepatoprotective activity	Leaves	Polyphenol-enriched fraction (400 mg·kg^{-1})	Oxidative stress and APAP-induced hepatotoxicity model (orally)	ROS/MAPKs/apoptosis axis and Nrf-2-related factor mediated antioxidant response	[45]
Cardiovascular protective activity	Leaves	Flavonoids extract (4 and 8 mg·kg^{-1})	AMI model (i.g.)	Inhibit the J spot downward of ECG Decrease LDH and CK in serum Enhance the activity of SOD and GSH-Px Reduce the production of MDA of myocardial tissue	[46]
Anti-hyperlipidaemic activity	Leaves	95% Alcohol extract (7.8 g·kg^{-1}) Alkaloids (600 and 900 mg·kg^{-1}) Total flavonoid glycosides (187.5mg·kg^{-1}·d^{-1})	HLP mice (i.g.)	Reduce TC and TG Increase the level of ApoAI, LCTA, SOD and NO Reduce TC, TG and LDL-C Increase HDL-C	[47] [48] [26]
Antipyretic activity	Barks Fruits Leaves	Methanol extract (200 and 400 mg·kg^{-1}) Methanol extract (400 mg·kg^{-1}) Water extract (8.4 and 16.8 g·kg^{-1})	Brewer's yeast-induced pyrexia test (orally) Dry yeast induced fever rat model (orally)	Reduce body temperature significantly	[5] [49]
Jaundice-relieving activity	Leaves	Water extract (5.85, 11.7 and 23.4 g·kg^{-1}) *n*-Butanol extract (23.4g·kg^{-1})	Cholestasis mice induced by ANIT(i.g.)	Reduce T-BiL and D-BiL Suppress the activity of ALT, AST and ALT in bile	[50] [51]
Anti-diabetic activity	Fruits	Chloroform extract Aqueous extract	*α*-Glucosidase enzyme inhibitory assay (*in vitro*)	IC_{50} 1262.82 μg·mL^{-1} IC_{50} 1367.56 μg·mL^{-1}	[7] [41] [52]
	Leaves	70% Methanol extract Vitexin (**23**) Isovitexin (**24**) Isorhamnetin-3-*O*-*β*-D-rutinoside (**15**)		IC_{50} 61.30 μg·mL^{-1} IC_{50} 244.0 μmol·L^{-1}, IC_{50} 266.2 μmol·L^{-1} IC_{50} 275.4 μmol·L^{-1}	
Other activities	Fruits Leaves	Chloroform extract (200 and 400 mg·kg^{-1}) 50% Ethanol extract	Open field and hole cross test (orally) Fibroblast increment test (*in vitro*)	Decrease of locomotor activity Antiaging activity	[41] [24]

The different components contained and different administration routes would weaken the comparability of antidiarrheal experiments. The antidiarrheal mechanisms of MPL hydro-methanol and petroleum benzene extracts are shown in Fig. 2.

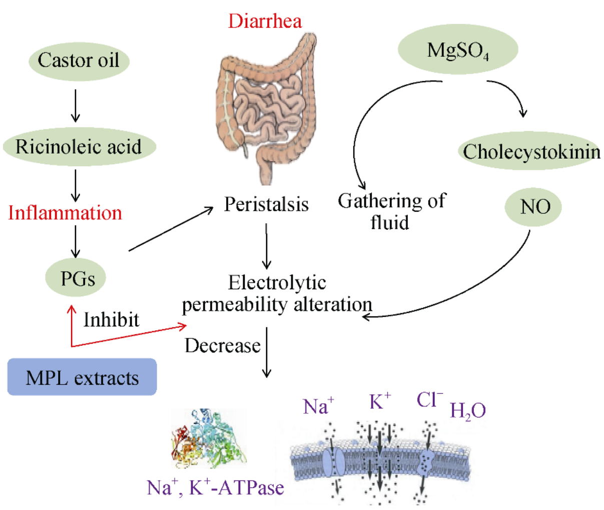

Fig. 2 The antidiarrheal mechanism of hydromethanol and petroleum benzene extracts of *Microcos paniculata* (MPL)

Antimicrobial and insecticidal activity

Aziz *et al.* [17] investigated the antibacterial activity of MPL fruits by employing agar disc diffusion test. With flucloxacilin (10 μg/disc) as positive control, the results implied that methanol extract exhibited antibacterial activity especially against gram negative bacteria, and the highest sensitivity was observed on *P. mirabilis* (zone of inhibition 28 mm). Likewise, both barks methanol extract and roots chloroform extract of MPL (2, 4 and 6 mg/disc) significantly slowed down the growth of gram negative bacteria [6, 16].

Additionally, methanol and chloroform extracts from MPL barks, fruits and roots as well as and microcosamine A (**35**) and microcosamine B (**36**) exhibited the potential larvicidal activity against the 4th instar *Culex quinquefasciatus* mosquito [6, 16-17, 27]. Similarly, *N*-methyl-6α-(deca-l′, 3′, 5′-trienyl)-3β-methoxy-2β-methylpiperidine (**31**) suggested moribund toxic and growth-inhibitory bioactivities on the 2th instar larvae of the mosquito *Aedes aegypti* [19]. Both fruits chloroform and aqueous extracts of MPL (50 mg·mL^{-1}) caused paralysis and death of *Pheretima posthuma* [7, 41].

The antimicrobial and insecticidal activity of MPL barks, roots, fruits and leaves may partly explain the traditional detoxification bioactivity of MPL. However, the underlying mechanism and phytochemical analysis of MPL extracts is not proposed. Further studies on the structure-activity relationship are necessary to ascertain its antimicrobial and insecticidal activity.

Anti-inflammatory and analgesic activity

Aziz *et al.* [41] investigated the anti-inflammatory activity of MPL extracts by protease inhibition assay in *vitro*. The results showed that IC_{50} of fruits aqueous extract, fruits methanol extract and barks methanol extracts were 285.47, 201.55 and 61.31 μg·mL^{-1}, respectively, while the IC_{50} of the Aspirin (positive control) was 24.46 μg·mL^{-1}. In xylene-induced ear edema and cotton pellet-induced granuloma formation test examined by Aziz [5], methanolic extract of MPL barks and fruits (200 and 400 mg·kg^{-1}) could suppress inflammation when compared with the diclofenac sodium treatment group (positive control), and fruits methanolic extract (400 mg·kg^{-1}) implied the highest inhibition of 36.97% for ear edema and 45.96% for granuloma formation. At the molecular level, LI *et al.* [44] evaluated the anti-inflammatory activity of apigenin *C*-glycosides from MPL leaves (10, 20 and 40 mg·kg^{-1}) by lipopolysaccharide (LPS)-induced acute lung injury (ALI) model in mice. Apigenin *C*-glycosides attenuated ALI through modulating toll-like receptor 4 (TLR4)/ transient receptor potential channel 6 (TRPC6), reducing the release of pro-inflammatory cytokines and regulating the expression of apoptosis-related factors. Further study on structure-activity relationship of apigenin *C*-glycosides and ALI attenuating activity need to be carried out.

The treatment for allergies of MPL barks, fruits and fruits may due to its inhibitory activity on inflammation. Oral treatment with methanol extract of MPL barks and fruits (200 and 400 mg·kg^{-1}) significantly reduced paw licking of mice induced by formalin [5]. The above extracts together with hydro-methanol and petroleum benzene extracts of MPL barks (200 and 400 mg·kg^{-1}, i.g.) and ethanol extract of MPL leaves (250 and 500 mg·kg^{-1}) were associated with the reduction of mice writhing induced by acetic acid [5, 8, 44]. Moreover, in mice tail immersion test, barks petroleum benzene extract (200 and 400 mg·kg^{-1}) suggested a significant increase in latency at 30 min, while barks methanol (400 mg·kg^{-1}) and fruits methanol extract (200 and 400 mg·kg^{-1}) suggested a significant increase in latency at 60 min compared with control group [5, 8]. In hot plate tests of mice, hydro methanol and petroleum benzene extracts (200 mg·kg^{-1}) of MPL barks suggested a significant increase in response latency at 30 min compared with control group following the treatment [8]. However, the exact mechanism of its analgesic activity needs further exploration.

Hepatoprotective activity

WU *et al.* [45] evaluated the potential mechanisms of the polyphenol-enriched fraction from MPL leaves on oxidative stress and acetaminophen (APAP)-induced hepatotoxicity. The results demonstrated that the fraction (400 mg·kg^{-1}, i.g.) possessed a hepatoprotective function mainly through dual modulating reactive oxygen species (ROS)/MAPKs/apoptosis axis and nuclear factor erythroid 2 (Nrf-2)-related factor mediated antioxidant response. Those data revealed the possible clinical potential of MPL leaves as a natural and functional food ingredient for the prevention of oxidative stress-induced hepatic injury. However, according to the extraction process, the equal dose of MPL leaves extract (15 g·kg^{-1}) used in that study was too high.

Cardiovascular protective activity

CHEN *et al.* [46] investigated the effect of MPL leaves on isoprenaline (ISO) induced acute myocardial ischemia (AMI) rats. After daily oral treatment with flavonoids of MPL leaves (4 and 8 mg·kg^{-1}) for 5 days, the J spot downward of ischemia's electrocardiogram (ECG) was significantly inhibited after 10 min of ISO injection. Moreover, flavonoids also significantly decreased the levels of lactate dehydrogenase (LDH) and creatine kinase (CK) in serum, accompanied by the decrease in malondialdehyde (MDA) and increase in superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) of myocardial tissue. Based on these findings, the antioxidant activity may be one of the mechanisms underlying the anti-AMI bioactivity of MPL leaves. However, the bioactive constituents responsible for cardiovascular protective activity of MPL extracts were not characterized in that study.

Anti-hyperlipidemic activity

Research by SUN *et al.* [47] found that supplementation with 95% alcohol extract of MPL leaves (7.8 g·kg^{-1}, i.g.) for 7 days significantly reduced both TC and TG in hyperlipidemia (HLP) bearing mice. In another study, administration of alkaloid fraction (600 and 900 mg·kg^{-1}, i.g.) of MPL leaves to HLP rats significantly increased the level of apolipoprotein (ApoAI), lecithin cholesterol acyltransferase (LCTA), superoxide dismutase (SOD) and NO, indicating that total alkaloid fraction could regulate blood lipids in multifaceted ways [48]. After treatment with 187.5 mg·kg^{-1}·d^{-1} (i.g.) flavonoid glycosides MPL leaves within 14 d to HLP mice, the serum LDL-C, TC and TG were significantly reduced, while the level of HDL-C was significantly increased [26]. However, the chemical analysis of these fractions in MPL leaves and the detailed mechanism were not elucidated, and the doses of alkaloids and flavonoids extracts used may be too high.

Antipyretic and jaundice-relieving activity

In brewer's yeast-induced pyrexia mice, barks methanol extract (200 and 400 mg·kg^{-1}) and fruits methanol extract (400 mg·kg^{-1}) exerted significant post-treatment antipyretic action by inhibiting PGs production [5]. In dry yeast induced fever rat model, water extract of MPL leaves (8.4 and 16.8 g·kg^{-1}) reduced body temperature to normal levels [49]. DAI [50] investigated jaundice-relieving activity on *n*-butanol (23.4 g·kg^{-1}) and water fractions (5.85, 11.7 and 23.4 g·kg^{-1}) of MPL leaves in cholestasis mice induced by *α*-naphthyl isothiocyanate (ANIT). The results suggested that these fractions have potential jaundice-relieving activity via significant reduction of serum total bilirubin (T-BiL), direct bilirubin (D-BiL), ALP, AST and ALT in comparison with control group [51]. Nevertheless, the doses of MPL leaves extract used in these researches were quite high and only single dose was used in *n*-butanol fraction. Future research on the relationship between antipyretic and jaundice-relieving activities of MPL leaves should be conducted.

Anti-diabetic activity

Aziz *et al.* [7, 41] evaluated the *in vitro* *α*-amylase inhibitory activity of chloroform and aqueous extract of MPL fruits, and their IC_{50} were 1262.82 and 1367.56 μg·mL^{-1} compared to 785.84 μg·mL^{-1} of the positive drug acarbose. Likewise, CHEN *et al.* [52] investigated the *α*-amylaes inhibitory activity of 70% methanol extract of MPL leaves along with vitexin (**23**), isovitexin (**24**) and narcissin (**15**), and their IC_{50} were 61.30 μg·mL^{-1}, 244.0, 266.2 and 275.4 μmol·L^{-1}, respectively, while the IC_{50} of acarbose was 1007.0 μmol·L^{-1}. However, the anti-diabetic activity of MPL only involved the exploration of *α*-amylase inhibitory activity *in vitro*, more *in vivo* studies are needed to reveal the anti-diabetic activity of compounds in MPL.

Other activities

The mice open field and hole cross test performed on MPL fruits showed that chloroform extract (200 and 400 mg·kg^{-1}) significantly depressed central nervous system by decreasing locomotor activity. Diazepam (1 mg·kg^{-1}) was used as a standard drug [41]. Besides, Dohi *et al.* [24] reported the anti-aging bioactivity of 50% ethanol extract of MPL leaves as skin external preparation. Consistent with the antioxidant activity, the studies may guide the development of cosmetics and skin care products of MPL leaves.

Toxicology

Acute toxicity in mice

The toxicological studies were important to understand the safety profile of traditional herbal drugs. MPL leaves had always been used as an edible health care food and herbal tea, as well as preparing Chinese medicinal formulae by TCM physicians in folk. There were few clinical reports on its toxic or side effect. According to the guidelines of Organization of Economic Cooperation and Development (OECD), there were no signs of toxicity or behavioral changes observed during 14 d in mice administered as high as 4000 mg·kg^{-1} of both bark methanolic and fruit chloroform extracts of MPL [5, 41].

Cytotoxicity

Rahman *et al.* [44] and Aziz *et al.* [6, 16] measured the toxicity against brine shrimp nauplii of MPL extract. The LC_{50} of leaves ethanolic extract, roots chloroform extract, barks chloroform extract and fruits methanol extract were 60, 19.4, 73.3 and 52.7 μg·mL^{-1}, respectively, which were lower than the toxicity level of 1000 μg·mL^{-1}, indicating that potential cytotoxic compounds may exist in theses extracts. Research by Still *et al.* [29] suggested microgrewiapine A (**38**) from chloroform extracts of MPL stem bark, branches and leaves exerted cytotoxic activity against HT-29 human colon cancer cells with IC_{50} value of 6.8 μmol·L^{-1}, as well as nicotinic receptor antagonistic activity for both h*α*3*β*4 and h*α*4*β*2 receptor subtypes with the inhibition of and 74.0% ± 14.2% at 10 μmol·L^{-1}. The researches implied that alkaloids in MPL may have 58.2% ± 9.2% cytotoxic activity against certain cells, but only single dose (10 μmol·L^{-1}) was used in nicotinic receptor antagonistic activity study.

Conclusion and Future perspectives

The available information on phytochemistry and pharmacology of MPL bark, fruits, roots and leaves provides new thoughts for its ethnopharmacological research. The flavonoids are considered as the main bioactive compounds in MPL leaves [26, 35]. The digestion promoting activity of MPL leaves extracts may correspond to its traditional use for "resolving food stagnation" and "abdominal distension and dyspepsia". The antidiarrheal activity of MPL leaves, fruits and barks is partly in line with the traditional use for "diarrhea dues to damp-heat". The anti-inflammatory, analgesic, antipyretic, antimicrobial, insecticidal and jaundice-relieving activities of MPL bark, fruits, roots and leaves extracts reported are partly consistent with the traditional effect of "heat-clearing and detoxifying, dampness and jaundice removing".

Based on the literature review above, some future perspectives of MPL should include the following:

1. The flavone *C*-glycosides are regarded as bioactive constituents in MPL leaves, but their activities have not been fully investigated *in vivo*. The structure-activity relationship, in-depth molecular mechanisms responsible for the beforementioned pharmacological activities of flavone *C*-glycosides need further research.

2. The roots, barks and fruits extracts of MPL revealed significant brine shrimp lethality bioassay, and the piperidine alkaloids may be responsible for its cytotoxicity. However, only a few researchers explored the toxicity of the alkaloids and extracts from of MPL, enough cytotoxic investigation will help to discover novel insecticides and bacteriostatic agent.

3. The absorption distribution metabolism excretion toxicity (ADMET) evaluation of these isolated compounds need further research to find the bioactive compounds in MPL and clarify the mechanism of MPL. The standardization of extracts and extract fractions with bioactive marker compounds are required to reveal the therapeutic potential of MPL leaves. Additionally, more *in vivo* and clinical studies may provide some clues about the corresponding relationship between pharmacological activities and traditional uses of MPL bark, fruits, roots and leaves extracts.

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Cite this article as: JIANG Ying-Qun, LIU E-Hu. *Microcos paniculata*: a review on its botany, traditional uses, phytochemistry and pharmacology [J]. *Chin J Nat Med*, 2019, **17**(8): 561-574.