Research Progress of Total Flavonoids from Plants in Trib. Lorantheae

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Abstract Trib. Lorantheae is one of the important medicinal plants in traditional medicine. There are 41 genera, 6 genera of which are produced in China, mainly distributed in Southwest China, South China and Central South China. There are many kinds of plants in this family, and 22 species can be used as Chinese medicinal materials in China. The branches and leaves of Trib. Lorantheae are rich in flavonoids, alkaloids, terpenoids, polysaccharides, organic acids and other functional substances, among which flavonoids are one of the important chemical components to exert pharmacological activity, and play an important role in hypoglycemic, lipid-lowering, anti-inflammatory, anti-tumor, anti-oxidation, anti-osteoporosis and so on. In this paper, the chemical composition, extraction method, component analysis and pharmacological action of flavonoids in Trib. Lorantheae plants were reviewed, in order to provide scientific reference for further development and clinical application of flavonoids in Trib. Lorantheae plants.

Key words Trib. Lorantheae; Total flavonoids; Extraction techniques; Analytic procedure; Pharmacological effect

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Trib. Lorantheae refers to semi-parasitic shrubs belonging to 41 genera of Loranthaceae, recorded in *Flora of China*[1], of which 6 genera are produced in China, mainly distributed in Southwest China, South China and Central South China. There are many kinds of plants in this family, and 22 species (including varieties) can be used as Chinese medicinal materials in China. Among them, *Taxillus chinensis* (DC.) Danser is most widely used[2-4]. As a medicinal material, Herba Talxilli, is listed as the top grade, and called "parasite on mulberry". Herba Talxilli included in the 2020 edition of *Pharmacopoeia of the People's Republic of China* (hereinafter referred to as *Chinese Pharmacopoeia*) refers to dry leafy stems and branches of *T. chinensis* (DC.) Danser in Loranthaceae. It is neutral in nature, bitter and sweet in taste, and attributive to the liver and kidney meridians. It has the effects of expelling wind-damp, nourishing liver and kidney, strengthening bones and muscles, and preventing miscarriage. It is often used to treat rheumatic arthralgia, soreness of waist and knees, weakness of bones and muscles, and deficiency of liver and kidney[5-7].

Flavonoids are widely distributed in nature, with a wide variety and extensive pharmacological activity, and serve as important effective components in Chinese herbs[8]. Flavonoids are main chemical components, as well as main effective components of plants in Trib. Lorantheae. In recent years, there have been many reports on the chemical constituents, extraction techniques, component analysis and pharmacological effects of flavonoids from Trib. Lorantheae, but there is no systematic review of related research. Therefore, this paper sorted out and summarized research progress in chemical composition, extraction techniques, component analysis and pharmacological action of flavonoids from plants belonging to Trib. Lorantheae, hoping to provide reference for their resource development and medicinal utilization.

Flavonoids in Trib. Lorantheae

Flavonoids are one type of the main active components of plants in Trib. Lorantheae, mainly flavonols, most of which are the main medicinal substances of plants in Trib. Lorantheae, such as quercitrin, avicularin and quercetin. At present, it has been found that there are 39 flavonoids isolated from plants in Trib. Lorantheae (Table 1), which can be divided into flavonols, flavanes, flavonones, flavonoids and chalcones according to different parental nuclei. In specific, there is 1 flavonoid (compound 1), 1 chalcone (compound 2), 9 flavane compounds (compounds 3-11), 7 flavonone compounds (compounds 12-18), and 21 flavonol compounds (compounds 19-39)[9-30].

Methods for extracting flavonoids from Trib. Lorantheae

Improving the extraction rate of total flavonoids from Trib. Lorantheae by adopting efficient extraction processes is of great significance for component analysis and pharmacological activity research. At present, the main methods for extracting total flavonoids from Trib. Lorantheae plants include heating reflux extraction, ultrasonic-assisted extraction, *etc.* (Table 2).

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Table 1 Flavonoids in Trib. Lorantheae

No.	Classification	Compound	Species	Reference
1	Flavonoids	Luteoloside	*T. chinensis*	[9]
2	Chalcones	Naringenin chalcone	*T. chinensis*	[9]
3	Flavanes	(2S)7,3'-O-Diformyl-5,4'-dihydroxyflavone	*H. parasitica*	[10]
4		(2S)-7-O-Formyl-5,3',4'-trihydroxyflavone	*H. parasitica*	[10]
5		(2S)-7,4'-O-Diformyl-5,3'-dihydroxyflavone	*H. parasitica*	[10]
6		Epicatechin	*H. parasitica*	[10]
7		Procyanidin B1	*D. pentandra*	[11]
8		Procyanidin B3	*D. pentandra*	[11]
9		Epigallocatechin gallate	*T. chinensis*	[9]
10		Gallocatechin	*T. nigrans*, *T. delavayi*	[12-13]
11		Catechin	*H. Parasitica*, *T. chinensis*, *T. nigrans*, *T. sutchuenensis*, *T. delavayi*, *D. pentandra*, *S. ferruginea*	[9,11-17]
12	Flavonones	Isosakuranetin	*T. sutchuenensis*	[18]
13		Viscumneoside I	*T. sutchuenensis*	[18]
14		Homoeriodictyol 7-O-β-D-glucoside	*T. sutchuenensis*	[18]
15		Taxifolin	*T. chinensis*	[9]
16		Naringenin	*T. chinensis*	[9]
17		4"-O-Acetylquercitrin	*S. ferruginea*	[19]
18		5,7,3',4'-Tetrahydroxyflavone	*H. parasitica*	[11]
19	Flavonols	7-O-Methylquercetin-3-O-α-L-rhamnopyranoside	*L. tanakae*	[20]
20		Rhamnetin-3-O-β-D-glucopyranoside	*L. tanakae*	[20]
21		7-O-Methyl-kaempferol -3-O-α-L-rhamnopyranoside	*L. tanakae*	[20]
22		5,3',4'-Trihydroxy-7-methoxyflavone 3-O-(2″-rhamnosyl glucoside)	*L. tanakae*	[20]
23		Loranthflavonoside A	*L. tanakae*	[20]
24		Rhamnetin-3-O-α-L- rhamnoside	*L. tanakae*	[21]
25		Rhamnocitrin-3-rhamnoside	*L. tanakae*	[21]
26		Quercetin-3,3′,4′-trimethylether	*T. sutchuenensis*	[18]
27		Kaempferol-3,7-bisr hamnoside	*T. sutchuenensis*	[18]
28		Quercetin-3-O-(6"-galloyl)-β-D-glucoside	*T. nigrans*, *T. levinei*, *T. sutchuenensis*	[16,22,27-28]
29		Quercetin-3-O-(6"-galloyl)-β-D-galactoside	*T. nigrans*, *T. sutchuenensis*	[12,15]
30		Kaempferol	*T. chinensis*, *L. tanakae*	[9,22]
31		Kaempferitrin	*T. sutchuenensis*	[15]
32		Afzelin	*L. tanakae*, *T. chinensis*, *S. parasitica*	[15,25,29]
33		Isoquercitrin	*T. sutchuenensis*, *T. chinensis*, *T. nigrans*, *T. levinei*	[9,12,22-23]
34		Hyperin	*T. sutchuenensis*, *T. chinensis*	[9,23]
35		Quercetin-3-O-β-D- glucuronide	*T. chinensis*, *T. levinei*, *T. nigrans*, *T. sutchuenensis*	[9,15]
36		Quercitrin	*T. sutchuenensis*, *T. chinensis*, *S. parasitica*, *T. maclurei*, *L. tanakae*, *H. parasitica*, *S. ferruginea*, *D. pentandra*	[9,14,19,21,23-28]
37		Quercetin	*T. sutchuenensis*, *T. chinensis*, *S. parasitica*, *T. maclurei*, *S. ferruginea*, *D. pentandra*	[9,19,23-26,28-29]
38		Rutin	*T. sutchuenensis*, *T. maclurei*, *S. parasitica*, *T. chinensis*, *T. nigrans*	[9,12,23,26]
39		Avicularin	*T. chinensis*, *T. sutchuenensis*, *T. nigrans*, *S. parasitica*	[12,14,24-25,30]

The heating reflux extraction method is a traditional extraction method for flavonoids. Scholars often use a combination of single factor methods and orthogonal experiments or response surface methodology to optimize the extraction process of flavonoids from Trib. Lorantheae plants, and the extraction rate of total flavonoids from Trib. Lorantheae plants is used as an indicator to improve the process. Research has found that when using orthogonal experiments to optimize the heating reflux extraction process, the order of various factors is: extraction temperature > extraction reagent concentration > extraction time > reflux times > ethanol addition[32-36]. The reflux extraction of total flavonoids from plants in Trib. Lorantheae is simple and easy to operate, but its industrial application is affected by too long extraction time, many impurities in the products, low extraction efficiency and poor economic benefits.

Table 2 Process parameters for extracting flavonoids from Trib. Lorantheae using different methods

Extraction method	Process optimization method	Optimized extraction process	Extraction rate	Species	Extracting object
Water decoction method	Single factor method combined with orthogonal experiment method[31]	Decocting with 10 times of water for 3 times, 2.0 h each time.	0.67%	*T. chinensis*	Total flavonoids
Heating reflux extraction method	Single factor method combined with orthogonal experiment method[32]	Extracting under ethanol concentration 70%, solid-liquid ratio 1∶20 and extraction temperature 80 ℃, twice, 1.5 h.	5.5%	T. chinensis	Total flavonoids
	Single factor combined with response surface method[33]	Extracting under volume fraction of ethanol 40% and liquid-solid ratio 40∶1 with refluxing twice, 1 h each time.	1.15%	*T. chinensis*	Total flavonoids
	Single factor method combined with orthogonal experiment method[34]	Extracting under ethanol concentration 50%, solid-liquid ratio 1∶30 and extraction temperature 70 ℃ for 2 h.	5.45mg/g	*T. chinensis*	Total flavonoids
	Single factor method combined with orthogonal experiment method[35]	Leaves: Extracting under ethanol concentration 70%, solid-liquid ratio 1∶35 and 80 ℃ for 3 h; optimal extraction conditions for braches: extracting under ethanol concentration 50%, solid-liquid ratio 1∶15 and 80 ℃ for 3 h.	Leaves: 9.47% Branches: 5.25%	*S. parasitica*	Total flavonoids
	Single factor method[36]	Extracting under ethanol concentration 60%, solid-liquid ratio 1∶25 and extraction temperature 60 – 70 ℃ for 3 h.	Leaves: 7.9% Branches: 6.01%	*S. parasitica*	Total flavonoids
Ultrasonic-assisted extraction	Single factor combined with response surface method[37]	Extracting with the assistance of ultrasound at 143.71 W for 31.96 min, under ethanol concentration 48.05%, liquid-solid ratio 50∶1 and extraction temperature 60 ℃.	49.13 mg/g	T. chinensis	Total flavonoids
	Single factor method combined with orthogonal experiment method[26]	Extracting under ethanol concentration 40% and solid-liquid ratio 1∶25 for 75 min.	*T. chinensis*: 38.40 – 43.77 mg/g *S. parasitica*: 13.34 – 26.05 mg/g *T. maclurei*: 28.38 – 29.96 mg/g	*T. chinensis* *S. parasitica* *T. maclurei*	Total flavonoids
	Single factor method combined with orthogonal experiment method[38]	Extracting under ethanol concentration 75%, solid-liquid ratio 1∶20 and extraction temperature 25 ℃ for 60 min.	55.08%	*L. tanakae*	Total flavonoids
	Single factor method combined with orthogonal experiment method[39]	Branches: ethanol concentration 60%, ultrasonic extraction time 30 min, ultrasonic extraction temperature 45 ℃, and solid-liquid ratio 1∶25; Leaves: ethanol concentration 70%, ultrasonic extraction time 20 min, ultrasonic extraction temperature 45 ℃, and solid-liquid ratio 1∶25.	Branches: 5.24 – 5.26 mg/g Leaves: 27.14 – 32.08 mg/g	*T. chinensis*	Total flavonoids
	Single factor method combined with orthogonal experiment method[40]	Stems and branches: 0.5 g, ethanol concentration 60%, ultrasonic extraction time 30 min, ultrasonic extraction temperature 45 ℃, and solid-liquid ratio 1∶25; leaves: 0.5 g, ethanol concentration 70%, ultrasonic extraction time 20 min, ultrasonic extraction temperature 45 ℃, and solid-liquid ratio 1∶25.	Branches: 7.63 – 7.86 mg/g Leaves: 31.52 – 32.08 mg/g	*T. chinensis*	Total flavonoids
	Single factor method combined with orthogonal experiment method[41]	Stems and branches: 0.5 g, ethanol concentration 60%, ultrasonic extraction time 30 min, ultrasonic extraction temperature 45 ℃, and solid-liquid ratio 1∶25; leaves: 0.5 g, ethanol concentration 70%, ultrasonic extraction time 20 min, ultrasonic extraction temperature 45 ℃, and solid-liquid ratio 1∶25.	Stems: 4.10 – 7.82 mg/g Branches: 18.33 – 32.08 mg/g	*T. chinensis*	Total flavonoids
	Single factor method combined with orthogonal experiment method[42]	Extracting with the assistance of ultrasound for 35 min with 80% ethanol as solvent, at ultrasonic extraction temperature of 55 ℃ and solid-liquid ratio of 1∶15.	22.97 mg/g (parasitizing on willow trees), 21.45 mg/g (parasitizing on Chinese cassia trees), 19.91 mg/g (parasitizing on mulberry trees)	*T. chinensis*	Total flavonoids

Ultrasonic-assisted extraction is a new extraction technique for extracting flavonoids. Compared with solvent extraction, ultrasonic-assisted extraction of total flavonoids from Trib. Lorantheae plants can reduce the amount of solvents, shorten extraction time and has higher extraction efficiency. In order to obtain the best extraction technique of total flavonoids from Trib. Lorantheae plants, scholars optimized and improved the method by single factor combined with response surface method or orthogonal experiments, which effectively improved the extraction efficiency[37]. It was found that when orthogonal tests are used to optimize ultrasonic-assisted extraction, the order of various factors is: ultrasonic time > ultrasonic power > ethanol concentration[26,37-42]. Ultrasonic-assisted extraction is relatively simple, takes a short time and does not need heating, but the industrial application still needs to solve the problems of environmental pollution and amplification of ultrasonic equipment.

Analysis Methods for Flavonoids in Trib. Lorantheae

At present, there are many methods that can be used to analyze flavonoids, and the main methods commonly used to analyze flavonoids in Trib. Lorantheae plants are ultraviolet spectrophotometry, high performance liquid chromatography and UPLC-MS method.

Ultraviolet spectrophotometry

The most important application of ultraviolet spectrophotometry (UV method) in the analysis of flavonoids is quantitative analysis. Su *et al.*[35] determined the total flavonoid content in branches of *Scurrula parasitica* L. by the UV method, and the content was calculated using rutin as the standard. The average yield of total flavonoids was 9.47% in *S. parasitica* leaves and 5.25% in branches. Qin *et al.*[43] established a UV method to determine the total flavonoid contents of *T. chinensis*, *Helixanthera parasitica* Lour. and *Macrosolen cochinchinensis*. The total flavonoid contents of three species in Trib. Lorantheae were measured to be 7.22 – 21.92, 22.63 – 58.90, and 7.60 – 22.15 mg/g, respectively. Jia *et al.*[44] established a UV spectrophotometry to determine the contents of total flavonoids in Herba Talxilli from different hosts. The contents of total flavonoids in Herba Talxilli from loquat and peach trees were measured to be 30.46 and 37.98 mg/g, respectively. The UV method is one of the commonly used methods for determining flavonoid contents, with simple operation, wide applicability, good accuracy, precision, and reproducibility.

UPLC method

The HPLC method is an important component separation and analysis method developed in combination with modern science and technology, commonly used for flavonoid content determination and component analysis. Cao *et al.*[45] established a fingerprint of Shoutai Pill Compound using HPLC and identified 36 characteristic peak components, of which 7 were flavonoids of *T. chinensis*, including characteristic components of rutin, quercitrin and quercetin. Song *et al.*[46] used the HPLC method to determine the content of quercetin in *Viscum ovalifolium*, and found that the content of quercetin was 0.28 mg/g. HPLC has the advantages of high separation efficiency, fast analysis speed, and high sensitivity, and is widely used in the analysis and content determination of components in traditional Chinese medicines.

UPLC-MS technique

The UPLC-MS technique combines the advantages of strong chromatographic separation ability and strong mass spectrometry qualitative ability. It can accurately measure molecular weight and determine molecular formula, and is crucial for the structural identification of flavonoids. Liang *et al.*[9] used UPLC-Q-Exactive-MS to identify 10 types of flavonoids and glycosides in *T. chinensis*, including quercetin-3-O-glucuronide, isoquercetin, catechin, kaempferol, naringin, hyperin, dihydroquercetin, catechin gallate, rutin, and naringenin chalcone. Wu *et al.*[47] established a UFLC-QTRAP-MS/MS method for determining the contents of 33 active ingredients in *T. sinensis*, including flavonoids. The results showed that the content distribution order of quercetin 3-O-glucoside, hyperoside, rutin, isoquercetin, quercetin and avicularin in different parts was leaf > stem branch. In addition, UPLC-MS has made significant progress in analyzing the composition and content determination of metabolites in medicinal plants. When using UPLC-MS to determine and compare the flavonoid metabolites of *T. sinensis* parasitizing on *Morus alba*, *Liquidambar formosana*, and *Clausena lansium*, it was found that there were 23 differential metabolites in *T. chinensis* parasitizing on *M. alba*, compared to those parasitizing *L. formosana*, and *C. lansium*. Through comparison, it was found that there were 11 unique differential metabolites in *T. chinensis* parasitizing *M. alba*[48]. The UPLC-MS technique is fast, highly sensitive, and requires less reagents for analyzing components. Therefore, it will gradually become the main analysis method for flavonoids in Trib. Lorantheae plants.

Pharmacological Effects of Flavonoids in Trib. Lorantheae

The total flavonoids in Trib. Lorantheae play important roles in pharmacological effects such as hypoglycemic, lipid-lowering, uric acid-lowering, anti-inflammatory, anti-tumor, antioxidant, anti-osteoporosis and antibacterial. With more in-depth research on the pharmacological effects of medicinal plants of Trib. Lorantheae, great progress has been made in the study of their related mechanisms, providing more scientific theoretical support for the clinical application of total flavonoids of Trib. Lorantheae.

Hypoglycemic, lipid-lowering and uric acid-lowering effects

It has been reported that flavonoids can inhibit diabetes. The total flavonoids of *T. chinensis* could reduce blood sugar by inhibiting the activity of α-glucosidase, and the inhibitory effect was enhanced with the increase of dosage[49]. Meanwhile, its different doses also had good hypoglycemic effect on diabetic mice induced by streptozotocin, and the hypoglycemic effect was more obvious in the high-dose group[50]. In the research of lipid lowering, Wang *et al.*[51] found that quercetin (37) and avicularin (39) in *T. chinensis* could inhibit fatty acid synthase (FAS) and reduce body weight in rats, and the extract of *T. chinensis* could react with different sites on FAS, thus playing a role in lowering lipid. Studies have shown that the total flavonoids of *T. chinensis* also

have good uric acid-lowering activity, mainly by inhibiting the activity of xanthine oxidase (XOD), reducing serum levels of UA, XOD, Cr, and BUN, thereby exerting therapeutic effects on gout and protecting the kidneys[52-53].

Anti-inflammatory effect

A large number of reports show that many kinds of flavonoids from Trib. Lorantheae have anti-inflammatory activity. Ren *et al.*[54] found that rhamnetin-3-O-α-L-rhamnoside and enriched total flavonoids in the flavonoids of *Loranthus tanakae* played an anti-inflammatory role by down-regulating NF-κB, inhibiting NLPR3 and activating Nrf2-mediated inflammatory reaction. The study by Wang *et al.*[55] showed that the high- and medium-dose groups of total flavonoids from *T. chinensis* could significantly improve the degree of toe swelling and systemic symptoms in rats with adjuvant arthritis, as well as reducing immune organ coefficient and contents of serum IL-6 and TNF-α and increasing content of IL-10, thereby achieving anti-inflammatory treatment effects.

Antioxidant effects

The antioxidant effect of flavonoids mainly improves the cellular microenvironment and maintains body health by clearing free radicals and peroxides or reducing their production. Research has found that total flavonoids of *T. chinensis* have good antioxidant activity. They exhibit good activity in clearing DPPH and ABTS + free radicals, while also exhibiting certain reduction and *in-vitro* antioxidant abilities, and their activity increases with concentration. They can be utilized as natural antioxidants[26,37,56]. In addition to *T. chinensis*, the total flavonoids of *S. parasitica* and *Tolypanthus maclurei* can also scavenge DPPH free radicals, and the antioxidant capacity of FRAP ranked as *T. chinensis* > *T. maclurei* > *S. parasitica*[26]. Chen[57] found that by measuring the POV and MDA values of lard, it indicated that the flavonoids from leaves of *S. parasitica* had a certain antioxidant effect.

Anti-osteoporosis effect

Li *et al.*[58] showed that the total flavonoids of *T. chinensis* can effectively prevent bone loss, inhibit bone resorption, promote bone formation, and improve microstructure to prevent formic acid (RA)-induced gonadal damage and compensatory splenic hyperplasia in rats. Meanwhile, improving the negative balance of bone metabolism could play a role in treating formic acid (RA)-induced osteoporosis (OP) in rats. Wang *et al.*[59] found that the total flavonoids of *T. chinensis* could effectively prevent the microstructure changes of bone tissue caused by retinoic acid, increase the content of Ca^{2+} in rat serum, and reduce the levels of ALP and TRAP. For ovariectomized osteoporosis model rats, they could improve bone microstructure and increase serum Ca^{2+}, E2, OPG, RANKL and TGF-β1 level, and reduce ALP and IL-6 levels, thereby achieving a therapeutic effect.

Antitumor effect

In recent years, the impact of flavonoids on the growth, differentiation, apoptosis and drug resistance of tumor cells has become a hot research topic, and especially, new breakthroughs have been made in the treatment of leukemia with flavonoids and polyphenols in plants[60]. Xiao *et al.*[61-63] found that the total flavonoid extract of *S. parasitica* (Nispex) could significantly inhibit the proliferation and induce apoptosis of human tumor cells, and it was more sensitive to the proliferation of tumor cells. The total flavonoid extract of *S. parasitica* (Nispex) hosted by *Nerium indicum* might induce the apoptosis of CA46 cells by inhibiting the NF-κB signaling pathway, and it also had a strong inhibitory effect on the proliferation of HL-60 cells.

Other effects

RAJA CHANOA *et al.*[10] found that the mixture of flavonoids (2S)-7-O-formyl-5,3',4'-trihydroxyflavone and (2S)7,3'-O-diformyl-5,4'-dihydroxyflavone and (2S)-7,4'-O-diformyl-5,3'-dihydroxyflavone extracted from *H. parasitica* had significant antimalarial activity against *Plasmodium falciparum*. Chen[64] found that compound avicularin (4) extracted and separated from *T. sutchuenensis* had obvious diuretic effect.

Conclusions

The plant resources of Trib. Lorantheae are abundant and widely distributed. They contain complex chemical components, and have diverse pharmacological activity and thus have great potential for development. Flavonoids, as their main pharmacological active ingredients, have various pharmacological effects such as hypoglycemic, lipid-lowering, uric acid-lowering, anti-inflammatory, antioxidant, anti-osteoporosis, anti-tumor and antibacterial. With the continuous deepening of relevant research, the development and research of flavonoids in Trib. Lorantheae plants have great potential in the field of medicine. Although there have been many studies on the extraction process, analytical methods, chemical composition, and pharmacological effects of flavonoids in Trib. Lorantheae plants, research on the formulation development, pharmacokinetics, and biochemical synthesis of flavonoids in Trib. Lorantheae plants is still not in-depth enough. Moreover, plants in Trib. Lorantheae have the characteristic of semi-parasitism, and contain diverse flavonoid components, and there are complex components that exert pharmacological activity. Their active components may be influenced by hosts, or multiple components may jointly exert a certain pharmacological activity or a single component may exert multiple pharmacological activity. Therefore, it is necessary to study the interrelationships among their components, hosts and pharmacological activity.

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