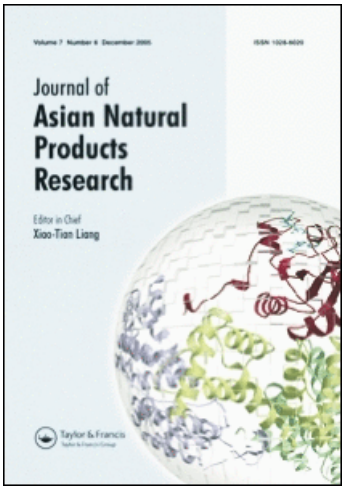

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ETHNOPHARMACOLOGICAL INVESTIGATIONS ON *THALICTRUM* PLANTS IN CHINA

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Thalictrum (Ranunculaceae) is an extremely abundant medicinal plant source. Due to their marked ethnopharmacological usages in folk medicine of China and the large number of potentially active chemical constituents, they may be a rich source for new chemicals for drug R&D. Here, an investigation on traditional functions and folk therapeutic uses of *Thalictrum* plants from China, as well as their main chemical constituents, was undertaken. It showed that 43 *Thalictrum* plants have long been used as folk medicine to treat many diseases in different races of China. In addition, the correlation between folk therapeutic effects and chemical constituents, and the modern pharmacological activities, are discussed as well as the prospect of isolation and development of new drugs from this genus of plants.

Keywords: *Thalictrum*; Ethnopharmacological investigation; Traditional function; Folk therapeutic effect

INTRODUCTION

As drugs of natural origin now play an ever more important role in medical and healthcare services, the ethnopharmacology of medicinal plants has attracted increasing attention in new drugs research and development. *Thalictrum* (Ranunculaceae) is an extremely abundant medicinal plant source. More than 200 species are distributed worldwide, with 67 species in the southwestern regions of China [1]. *Thalictrum* plants have a long history as folk medicine in the treatment of many kinds of diseases among various ethnic groups of China [2–4]. In some place, roots of *Thalictrum* were used as substitutes for *Rhizoma coptidis* to treat enteritis and dysentery [3].

Thalictrum plant is rich in benzylisoquinoline-derived alkaloids, at least 250 have been isolated from 60 species, and most of them show strong biological activities [5]. Here, we explore the ethnopharmacologic information and its relationship to the chemical constituents of *Thalictrum* plants, which can contribute greatly to the development of natural drugs. The results revealed that at least 43 species of *Thalictrum* have been used as folk medicinal plants, because of their special and proven therapeutic effects.

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ETHNOPHARMACOLOGICAL INVESTIGATIONS

Chemical Characterization of Thalictrum

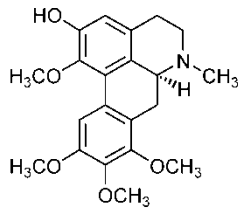
Thalictrum has attracted considerable interest mainly due to the production of benzylisoquinoline alkaloids. About 200 benzylisoquinoline alkaloids had been isolated from 30 *Thalictrum* plants of China. The main types of alkaloid include aporphines (**1**), protoberberines (**2**), bisbenzylisoquinoline dimers (**3**), aporphine-benzylisoquinoline dimers (**4**), protopines (**5**), pavines (**6**), diterpene alkaloids (**7**), phenanthrenes (**8**) and others (Fig. 1). In some recent research, many new alkaloids were isolated from *Thalictrum* plants [6–8].

Flavonoids have been found to be a minor or less abundant component in *Thalictrum* in previous studies, and only two flavonoids, 7,4′-di-*O*-β-allosyl-apigenin (**9**) [9] and 7-*O*-(6-acetyl-β-allosyl)-4′-*O*-(β-allosyl)apigenin (**10**) [9] were isolated from *T. squarrosum* and *T. minus*. However, in recent serial phytochemical investigations of our research group, two new flavonoids, kaempferol-3-*O*-[acetyl-α-L-arabinosyl-(1 → 6)]-β-D-glucoside (**11**) [10] and 4′-methoxyl-apigenin-7-*O*-[4-acetyl-α-L-rhamnosyl-(1 → 6)-β-D-glucosyl-(1 → 3)]-6-acetyl-β-D-glucoside (**12**) [11] as well as known flavonoids, kaempferol (**13**) [12], isoquercitin (**14**) [13], 4′-methoxyl-apigenin-7-*O*-[α-L-rhamnosyl-(1 → 6)]-β-D-glucoside (**15**) [14], kaempferol-3-*O*-[β-D-glucosyl-(1 → 3)-α-L-rhamnosyl-(1 → 2)]-β-D-glucoside (**16**) [11], 4′-methoxyl-apigenin-7-*O*-[4-acetyl-α-L-rhamnosyl-(1 → 6)]-β-D-glucoside (**17**) [11] and kaempferol-3-*O*-β-D-glucoside (**18**) [11] were isolated from *T. atriplex*, *T. smithii* and *T. przewalskii*. These studies indicate that flavonoids might be abundant in some species that are deficient in alkaloids.

Triterpene saponins, mainly including cycloartane-type and oleanane-type glycoside, have also been reported to be present in some species that contain less alkaloids. Examples of cycloartane-type glycosides are cyclofoetoside A (**19**) [15] and B (**20**) [16] from *T. foetidum*; thalicoside A (**21**) [17] and E (**22**) [18], thalicoside G_1 (**23**) and G_2 (**24**) [19], thalicoside H_1 (**25**) [20], thalicoside A_1 (**26**), A_2 (**27**) and A_3 (**28**) [21] from *T. minus*; smithioside A (**29**) [14] and B (**30**) [22] from *T. smithii*; squarroside A_1 (**31**), A_2 (**32**), B_1 (**33**), B_2 (**34**) [23], B_3 (**35**) and B_4 (**36**) [24], squarroside I (**37**) [25] and C (**38**) [26] from *T. squarrosum*; thalictosides D (**39**), E (**40**) and F (**41**) [27] from *T. thunbergii*. Examples of oleanane-type glycoside include foetoside C (**42**) [28,29] from *T. foetidum*; thalicoside B (**43**) [30] and D (**44**) [31] from *T. minus*; squarroside II (**45**), III (**46**) and IV (**47**) [25] from *T. squarrosum*. (Fig. 1)

Pharmacology of Thalictrum

Extracts and alkaloid isomers from *Thalictrum* are known to exhibit various pharmacological activities, including antitumor, antimicrobial, antimalarial, anti-inflammatory, antiamebic, anti-allergic, antiarrhythmic, Ca^{+} channel antagonistic and HIV antiviral activities. Triterpene saponins showed marked antitumor, immunomodulatory, antilipemic, cardiotonic and contraceptive activities [32]. Compound **27** showed inhibition on the fungus *Candida albicans*, and *Staphylococcus aureus in vitro* [21], whereas **42** showed antineoplastic activity [29]. Recent pharmacological research has shown that some triterpene saponins from *Thalictrum* plants hold potential immunosuppressive activity [33]. Acutiaporberine, a novel bisalkaloid derived from *T. acutifolium*, showed apoptosis-inducing activity for human non-small cell lung cancer (NSCLC) cell line, PLA-801 [34] and a cultured highly metastatic human lung cancer cell line 95-D [35].



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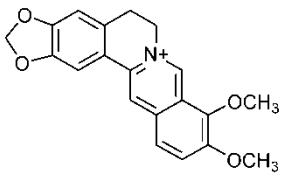

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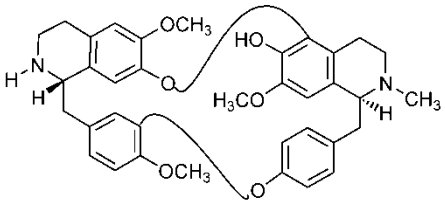

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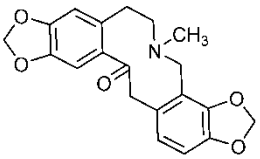

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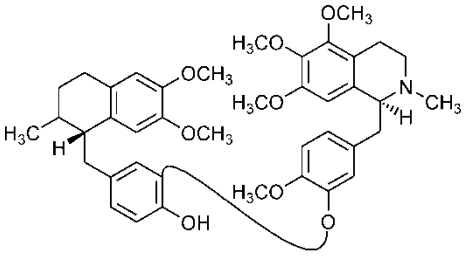

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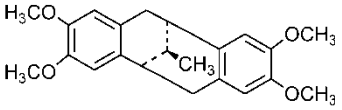

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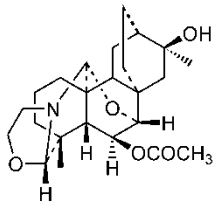

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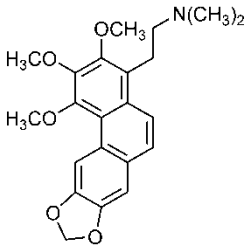

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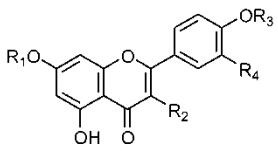
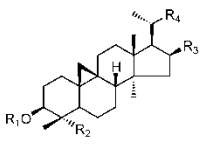
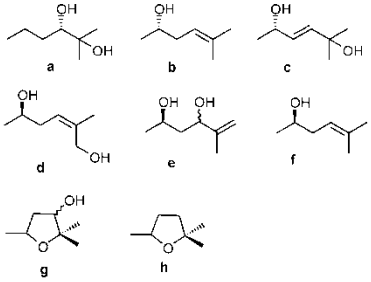
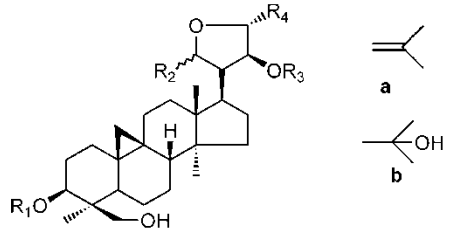


9 R_1=R_3=β-all R_2=R_4=H
10 R_1=6-O-acetyl-β-all R_3=β-all R_2=R_4=H
11 R_1=R_3=R_4=H R_2=O-3-O-acetyl-α-L-ara-(1-6)-β-D-glu
12 R_1=4-acetyl-α-L-rham-(1-6)-β-D-glu-(1-3)-6-acetyl-β-D-glu R_2=R_4=H R_3=Me
13 R_1=R_3=R_4=H R_2=OH
14 R_1=R_3=H R_2=O-β-D-glu R_4=OH
15 R_1=α-L-rham-(1-6)-β-D-glu R_2=R_4=H R_3=Me
16 R_1=R_3=R_4=H R_2=O-β-D-glu-(1-3)-α-L-rham-(1-2)-β-D-glu
17 R_1=4-acetyl-α-L-rham-(1-6)-β-D-glu R_2=R_4=H R_3=Me
18 R_1=R_3=R_4=H R_2=O-β-D-glu

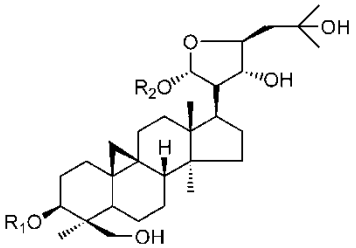




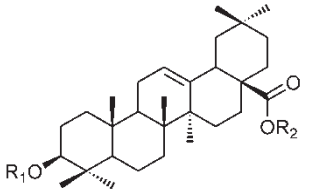
19 R_1=α-L-ara R_2= Me R_3=O-α-L-rham(1-6)-β-D-glu R_4= a
20 R_1=α-L-ara R_2= OH R_3=O-α-L-rham(1-6)-β-D-glu R_4= a
21 R_1=β-D-glu R_2=CH_2-O-β-D-glu R_3=OH R_4= b
22 R_1=β-D-glu R_2=CH_2-O-β-D-glu R_3=OH R_4= c
23 R_1=β-D-gala R_2=CH_2-O-β-D-glu R_3=OH R_4= d
24 R_1=β-D-gala R_2=CH_2-O-β-D-glu R_3=OH R_4= e
25 R_1=β-D-gala R_2=CH_2-O-β-D-glu R_3=OH R_4= g
26 R_1=β-D-glu R_2=CH_2-O-β-D-glu R_3=OH R_4= h
27 R_1=α-L-ara R_2=CH_2-O-β-D-glu R_3=OH R_4= f
28 R_1=α-L-ara R_2=CH_2-O-β-D-glu R_3=OH R_4= h
29 R_1=β-D-xyl-(1-2)-β-D-xyl R_2=CH_2OH R_3=OH R_4= a
30 R_1=β-D-xyl-(1-2)-β-D-glu R_2=CH_2OH R_3=OH R_4= a
37 R_1=α-L-ara R_2=Me R_3=H R_4= d



31 R_1=β-D-glu R_2=α-OH R_3=H R_4=a
32 R_1=β-D-glu R_2=β-OH R_3=H R_4=a
33 R_1=α-L-man-(1-6)-β-D-glu R_2=α-OH R_3=Me R_4=a
34 R_1=α-L-man-(1-6)-β-D-glu R_2=β-OH R_3=Me R_4=a
35 R_1=α-L-rham-(1-6)-β-D-glu R_2=β-OH R_3=H R_4=a
36 R_1=α-L-rham-(1-6)-β-D-glu R_2=α-OH R_3=H R_4=a
38 R_1=α-L-rham-(1-6)-β-D-glu R_2=α-O-β-D-glu R_3=H R_4=b
39 R_1=6-deoxy-α-L-man-(1-2)-O-[6-deoxy-α-L-man-(1-6)]-β-D-glu
R_2=α-O-β-D-glu-(1-2)-β-D-glu R_3=H R_4=b
40 R_1=6-deoxy-α-L-man-(1-2)-O-[6-deoxy-α-L-man-(1-6)]-β-D-glu
R_2=α-O-β-D-glu-(1-2)-O-[β-D-xyl-(1-6)]-β-D-glu R_3=H R_4=b



41 R_1=6-deoxy-α-L-man-(1-2)-O-[6-deoxy-α-L-man-(1-6)]-β-D-glu
R_2=β-D-glu-(1-2)-O-[β-D-xyl-(1-6)]-β-D-glu



42 R_1=β-D-xyl-(1-3)-α-L-rham-(1-2)-α-L-D-ara
R_2=β-D-glu-(1-6)-β-D-glu
43 R_1=α-L-rham-(1-2)-β-D-glu-(1-3)-α-L-D-ara
R_2=β-D-glu
44 R_1=α-L-rham-(1-2)-β-D-glu-(1-4)-α-L-D-ara
R_2=β-D-glu-(1-6)- β-D-glu
45 R_1=6-deoxy-α-L-man-(1-2)-O-[β-D-glu-(1-4)]-β-D-xyl
R_2=β-D-glu
46 R_1=6-deoxy-α-L-man-(1-2)-O-[β-D-glu-(1-4)]-β-D-xyl
R_2=β-D-glu-(1-6)-β-D-glu
47 R_1=β-D-glu-(1-4)-O-[β-D-glu-(1-3)-6-deoxy-α-L-man-(1-2)]-β-D-xyl
R_2=β-D-glu

FIGURE 1 Major constituents and typical compounds of *Thalictrum* from China.

Ethnopharmacology

Thalictrum plants have long been used as folk remedies in many parts of China. They exhibit marked ethnopharmacological effects on "clearing away pathogenic heat and dampness, detoxicating and antidiarrhea". Consequently, most of them were employed to treat dysentery, diarrhea, virus hepatitis, influenza, measles, carbuncle and boils and congestion of the eyes (Table I).

CONCLUSIONS

Ethnopharmacological investigation has revealed that the traditional therapeutic effects of *Thalictrum* plants are related to their chemical constituents and modern pharmacological activity [5].

Thalictrum plants used for diarrhea, dysentery and viral hepatitis were abundant in proberberine, a source of antipyrotic and antimicrobial activity. Plants showing antipyrotic, analgesic, sedative, anti-hypertension folk therapeutic effects, were often rich in aporphine and used to treat trauma, pain caused by rheumatism and carbuncle. Due to aporphine's modern pharmacological activities on antimalaria, anti-inflammatory, antitumor and cardiovascular system [36], these plants may be a potential source for medicine for diseases of the cardiovascular system and for cancer. Bisbenzylisoquinoline often occurred in plants that have traditional functions in antihypertension, antibacteria, anticancer, resisting arrhythmia, relieving spasm, relaxing muscles. These herbals were used to treat some diseases caused by heat evil in the traditional medical system, such as viral hepatitis, carbuncle and boils, jaundice and diarrhea. Bisbenzylisoquinolines [37] exhibit pharmacological activities in terms of antimalaria, anti-inflammatory, antitumor and for the cardiovascular system; plants containing these constituents are potential sources of drugs to treat cancer, malaria and cardiovascular system disease. Plants containing protopine had sedative and analgesic folk functions, and were used to treat pain caused by rheumatism, wound, carbuncle and boils. These plants may be developed as a sedative.

Plants rich in triterpene saponins, such as *T. smithii*, often function as regulator and facilitators of the flow of the vital energy, and in alleviating edema. Pharmacological

TABLE I Main constituents and traditional therapeutic effects of *Thalictrum* plants in China

Species	*Parts used*	*Main constituent*	*Traditional therapeutic effects*
Thalictrum acutifolium	I	**1**, **2**	General edema with yellowish tinge of the skin and eyes
T. alphinum	II, III	**2**, **3**	Clear away pathogenic heat and dampness, anti-bacteria, anti-dysentery
T. alphinum var. *elatum*	II		Chest tightness with nausea
	I		Malnutrition and infantile convulsion of children
T. aguilegifoli var. *sibiricum*		**1**, **3**	Carbuncle and boils, jaundice and diarrhea
T. atriplex	I, II	**1**, **2**, **3**, **5**, **11**, **13**, **14**	Virus hepatitis, carbuncle and boils
T. baicalense	II, III	**1**, **3**	Dysentery, congestion of the eyes
T. cirrhosum	II, III	**3**, **5**	Dysentery
T. cultratum	II, III	**1**, **2**, **3**, **4**	Dysentery, diarrhea, virus hepatitis, influenza measles, carbuncle and boils and congestion of the eyes
T. delavayi	II, III	**1**, **2**, **3**, **5**, **8**	Eye sore, toothache caused by the invasion of exogenous pathogenic fire and wind
T. faberi	II, III	**2**, **3**, **4**	Congestion of eyes
T. fargesii	I		Toothache, damatitis and infantile eczema
T. finetii	I	**1**, **2**, **3**, **5**	Dysentery
T. foetidum	II	**2**, **3**, **4**, **19**, **20**, **42**	Congestion of eyes, virus hepatitis, carbuncle and boils
T. foliolosum	II	**1**, **2**, **3**, **4**	Virus hepatitis, dysentery, congestion of eyes, heat type malnutrition of children, chickenpox, inadequate measles eruption
T. fortunei	II, I	**3**	Furuncle, herpes
T. glandulosissimum	II, III	**1**, **2**, **3**, **5**	Vexation caused by domination of heat-evil, dysentery, diarrhea, congestion of eyes, throat sore, carbuncle and boils
T. honanenae	I, II	**2**, **3**, **4**	Carbuncle and boils, toxic swelling
T. ichangense	I	**1**	Dispel pathogenic cold, antirheumatic, dispel caligo, dispel edema
	II		Convulsion in children, mycotic stomatitis of children
T. isopyroides	II, III	**1**, **3**, **5**	Dysentery
T. javanicum	II	**2**	Wound and trauma
	I	**3**, **4**, **7**	pain caused by rheumatism
T. macrorhynchum	I		influenza
T. megalostigma	II		Dysentery
T. microgynum	II	**2**, **3**, **5**	Wound and trauma

TABLE I – *continued*

Species	*Parts used*	*Main constituent*	*Traditional therapeutic effects*
	I		General edema with yellowish tinge of the shin, congestion of eyes
T. minus	II	**1**, **2**, **3**, **4**, **6**, **8**, **9**, **10**, **21**, **22**, **23**, **24**, **25**, **26**, **27**, **28**	Dysentery, diarrhea
T. minus var. *hypoleucum*	II		Toothache, acute cutitis, eczema
T. omeiense	II	**2**, **4**	Jaundice due to damp-heat pathogen, abdominal pain and dysentery, malaria, chills and fever
T. petaloideum	II	**1**, **2**, **5**	Jaundice, diarrhea, dysentery, oozy cutitis
T. przewalskii	II	**2**, **12**, **15**, **16**, **17**, **18**	Expel wind evil
	IV, V		Hepatitis, hepatomegaly
T. ramosum	I	**2**	Eye with yellowish tinge, heat type dysentery, jaundice
T.reniforme	II		Chancre
T. reticulatum	II	**1**, **3**	Influenza, cough
T. robustum	II		Dysentery, diarrhea
T. rutifolium	II		Clear away and purge pathogenic eat-fire, deprive the evil wetness and detoxicate
T. simplex	II, III	**1**, **2**, **3**, **5**, **7**	Dysentery by killing bacteria
T. simplex var. *brevipes*	I		Jaundice and dysentery
	IV, V		Hepatitis, hepatomegaly
T. smithii	I	**1**, **2**, **3**, **5**, **15**, **16**, **29**, **30**	Dizziness, bellyache, dysentery
T. squamiferum	I		Fever
T. squarrosum	I	**1**, **2**, **3**, **9**, **10**, **31**, **32**, **33**, **34**, **35**, **36**, **37**, **38**, **45**, **46**, **47**	Clear away pathogenic heat and detoxicate, Invigorate the stomach, induce iaphoresis
T. trichopus	II		High fever, infantile convulsion and cough of children caused by wind-heat evil attacking the lung
T. tuberiferum	II	**2**	Clear away pathogenic heat, anti-inflammation
T. uncinulatum	I	**1**, **2**	Early measles
T. virgatum	II		Disease of stomach
T. viscosum	II	**2**	Vexation caused by domination of heat-evil, dysentery, diarrhea, congestion of eyes, throat sore, carbuncle and boils

I = whole plant, II = root, III = rhizome, IV = flower, V = fruit.

research has shown that triterpene saponins from *Thalictrum* have contraceptive activities, which indicates that these plants may be a source for new medicines possessing estrogen-like and anti-osteoporosis efficacy as well as in treating cancer, hepatitis and immunoregulatory problems.

In summary, ethnopharmacologic information of *Thalictrum* plants can contribute greatly to the development of new drugs, since the use of traditional medicinal plants has been practiced for centuries and tested on a huge number of patients. Plants used for subduing and detoxicating carbuncles and boils may be a source of antitumor drugs. Plants used for eliminating pathogenic heat from the blood, releasing chest tightness and nausea may produce drugs for cardiovascular system diseases.

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