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Review

Toona sinensis: a comprehensive review on its traditional usages, phytochemisty, pharmacology and toxicology

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ABSTRACT

Toona sinensis (Juss.) M.Roem, Meliaceae, a deciduous plant native to eastern and southeastern Asia, is widely used in Traditional Chinese Medicine. This paper was aimed to summarize the current advances in traditional usage, phytochemistry, pharmacology and toxicology of *T. sinensis*. In this review, various types of data of *T. sinensis* are discussed in the corresponding parts of this paper, and perspectives for possible future studies of this plant are discussed. The main constituents of *T. sinensis* are terpenoids, phenylpropanoids and flavonoids, *etc.*, and its pharmacological activities include anti-tumor effects, antioxidant activities, anti-diabetic effects and anti-inflammatory effects. Although a series of phytochemical and pharmacological researches of this plant have been conducted, the active constituents and action mechanism of these activities should be also further explored. Furthermore, the present review also indicates that *T. sinensis* has potentials to develop into drugs for treating various diseases with high efficacy and low toxicity, particularly in cancer, diabetes and inflammatory disorders. In conclusion, the paper provides a full-scale profile of the traditional usage, phytochemistry, pharmacology and toxicology of *T. sinensis*, and also provides potential therapeutic uses and drug development prospects of this plant.

Introduction

Toona sinensis (Juss.) M.Roem [synonyms: *Cedrela sinensis* Juss, *xiāngchūn* (in Chinese)], belonging to Meliaceae family and popularly known as Chinese *toon* or Chinese mahogany, is a deciduous woody plant native to eastern and southeastern Asia (Liao et al., 2009). *T. sinensis* has a cultivation history more than 2000 years and is used as a vegetable source in China and Malaysia, and as animal fodder in India (Liao et al., 2007). *T. sinensis* is also widely used in Traditional Chinese Medicine (TCM) and various parts tissues of this plant have been used for a wide variety of diseases. The stems and leaves of TSR are traditionally used for the treatment of dysentery, enteritis, carminative and itchiness, *etc.* (Dong et al., 2013). The roots are used as correctives, the bark is used as astringent and depurative, and the fruits are used as astringent for the treatment of eye infections (Perry, 1980). Previous phytochemical investigations on this plant have revealed that the main constituents include terpenoids, phenylpropanoids, flavonoids and anthraquinones (Feng et al., 2007; Mu et al., 2007; Hsieh et al., 2008). Modern researches have also reported that *T. sinensis* possessed various pharmacological activities including anti-tumor effects, antioxidant effects, anti-diabetic effects, anti-inflammatory effects, antibacterial and antiviral effects. (Chen et al., 2007; Cheng et al., 2009; Wu et al., 2010) (Fig. 1).

Currently, *T. sinensis* has aroused considerable public interests in its medicinal and food uses, as well as novel terpenoids compounds. However, there is no systemic review on its recent traditional uses, chemical constituents, pharmacological activities and toxicological aspects; moreover, few current available literatures could suggest what working directions should be devoted to this plant in the future. Consequently, this paper was aimed to summarize the current advances in traditional usage, phytochemistry, pharmacology and toxicology of *T. sinensis*; furthermore, the present paper also provides some discussions to propose potential future development perspectives of this plant.

Traditional usage

Toona sinensis has been used as a natural herbal medicine for thousands years based on its reliable pharmacological effects. The medicinal use of this plant was firstly recorded in *Tang materia medica* which is a famous TCM monograph written in *Tang* dynasty in China (Anonymous, 1999; Wang et al., 2014). In Chinese folk medicine, *T. sinensis* was described as an herbal medicine with

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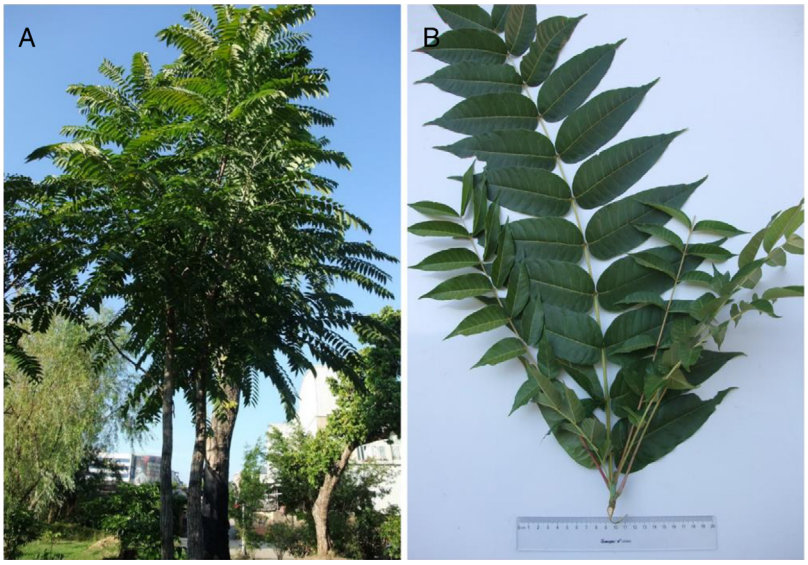


Fig. 1. *Toona sinensis* Roem. (A) Whole plant of *Toona sinensis*. (B) Leaves of *T. sinensis*.

good anti-inflammatory, detoxifying and hemostatic effects, and thus this plant was commonly used to treat enteritis, dysentery, urinary tract infection, leukorrheal diseases and skin itch (Anonymous, 1977, 1999; Li et al., 2006). Furthermore, due to its special onion-like flavor and wealth of carotene and vitamins B and C, the edible leaves and young shoots of *T. sinensis* are also delicious and nutritious food stuff in China and other Southeast Asia countries (Anonymous, 1999; Dong et al., 2013a).

Phytochemistry

In the early 1970s, compounds such as toosendanin (**1**), sterol and vitamins have been reported from the leaves and barks of *T. sinensis* in China (Anonymous, 1972). From then on, the phytochemical constituents of *T. sinensis* have been comprehensively investigated. So far, over one hundred compounds have been isolated and identified from this plant, including terpenoids, phenylpropanoids, and flavonoids. In this section, we described the main chemical components of *T. sinensis*, the corresponding isolation parts of these compounds were also concluded in Box 1.

Volatile oils

As well known that, special perfume is one of the characteristics of *T. sinensis* plant, thus previous researchers have investigated the volatile oils of this plant. For extraction of volatile oils from *T. sinensis*, the hydro-distillation and headspace solid-phase microextraction (HS-SPME) are commonly used, and gas chromatography coupled to mass spectrometry (GC–MS) is often used to identify the composition of volatile oil (Chen et al., 2009a; Li and Wang, 2014). Nowadays, over forty volatile components were isolated and identified from the tender shoots and leaves of *T. sinensis*. These constituents are mainly sesquiterpenes hydrocarbons, including caryophyllenes, β-caryophyllenes, copaenes and β-eudesmenes (Chen et al., 2009a; Dong et al., 2013b; Wu et al., 2014).

Terpenoids

Natural products is a large resource for finding novel structures for candidate drugs, and more than 40% of the marketed drugs are derived from the secondary metabolites in plant. Among them, the terpenoids are prominent secondary metabolites for discovering new candidate drugs with wide spectrum of activities, including hepatoprotective, antiviral, anti-bacterial, anti-inflammatory, and anti-tumor agents (James and Dubery, 2009; Zhou et al., 2017).

It is reported that this plant contains abundant terpenoids, and toosendanin (**1**) is the first triterpenoid isolated from this plant in 1972 (Anonymous, 1972). Till now, 59 terpenoids (including triterpenoids, diterpenes and sesquiterpenes) have been isolated from the leaves, shoots, barks and roots of *T. sinensis*, and limonoids triterpenoids are the characteristic constituents of *T. sinensis* (Box 1). The predominant terpenoids of this plant are the triterpenoids and include 3-*oxo*-12-*en*-28-oic acid (**2**) (Yang et al., 2013), α-betulin (**3**) (Dong et al., 2013a), ursolic acid (**4**), betulonic acid (**5**), betulic acid (**6**) (Yang et al., 2013), 11α-hydroxygedunin (**7**), 11β-hydroxygedunin (**8**), 7-deacetoxy-7α,11α-dihydroxygedunin (**9**), 7-deacetoxy-7α,11β-dihydroxygedunin (**10**), gedunin (**11**), 7-deacetoxy-7α-hydroxygedunin (**12**) (Mitsui et al., 2006), 7-deacetylgedunin (**13**) (Chen et al., 2017), 11-*oxo*-gedunin (**14**) (Mitsui et al., 2006), toonins A (**15**), proceranone (**16**) (Dong et al., 2013a), 6-acetoxyobacunol acetate (**17**), 7α-obacunyl acetate, 7α-acetoxy-dihydronomilin (**18**) (Luo et al., 2000), 11β-hydroxy-7α-obacunyl acetate (**19**), 11-*oxo*-7α-obacunyl acetate (**20**), 11-*oxo*-7α-obacunol (**21**), 11β-hydroxycneorin G (**22**), 11β-oxocneorin G (**23**) (Mitsui et al., 2004), cedrellin (**24**) (Luo et al., 2000), toonins B (**25**) (Dong et al., 2013a), grandifoliolenone (**26**) (Mitsui et al., 2007), bourjotinolone A (**27**) (Dong et al., 2013a), toona triterpenoids A (**28**), B (**29**), piscidinol A (**30**), hispidol B (**31**) (Mitsui et al., 2007), 20-hydroxy-24-dammaren-3-one (**32**), (20*S*)-3-*oxo*-tirucalla-25-nor-7-*en*-24-oic acid (**33**), (20*S*)-5α,8α-epidioxy-3-*oxo*-24-nor-6.9(11)-dien-23-oic acid (**34**), ocotillone (**35**), (20*S*,24*R*)-epoxydammarane-12.25-diol-3-one (**36**), (20*S*,24*R*)-epoxydammarane-3β,25-diolmarane-3β,25-diol

Box 1
Chemical compounds isolated from *Toona sinensis*.

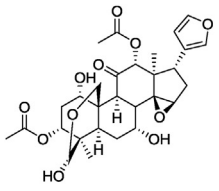
Classification	No.	Chemical component	Part of plant	References
Terpenoids	**1**	3-Oxo-12-en-28-oic acid	Leaves	Yang et al. (2013)
	2	α-Betulin	Roots	Dong et al. (2013a) Yang et al. (2013)
	3	Ursolic acid	Leaves	Yang et al. (2013)
	4	Betulonic acid	Leaves	Yang et al. (2013)
	5	Betulic acid	Leaves	Yang et al. (2013)
	6	11α-Hydroxygedunin	Barks	Mitsui et al. (2006)
	7	11β-Hydroxygedunin	Barks	Mitsui et al. (2006)
	8	7-Deacetoxy-7α,11α-dihydroxygedunin	Barks	Mitsui et al. (2006)
	9	7-Deacetoxy-7α,11β-dihydroxygedunin	Barks	Mitsui et al. (2006)
	10	Gedunin	Barks	Mitsui et al. (2006)
	11	7-Deacetoxy-7α-hydroxygedunin	Barks	Mitsui et al. (2006)
	12	7-Deacetylgedunin	Fruits	Chen et al. (2017a)
	13	11-Oxo-gedunin	Barks	Mitsui et al. (2006)
	14	Toonins A	Roots	Dong et al. (2013a)
	15	Proceranone	Roots	Dong et al. (2013a)
	16	6-Acetoxyobacunol acetate	Leaves	Luo et al. (2000)
	17	7α-Acetoxy-dihydronomilin	Leaves	Luo et al. (2000)
	18	11β-Hydroxy-7α-obacunyl acetate	Leaves	Mitsui et al. (2004)
	19	11-Oxo-7α-obacunyl acetate	Leaves	Mitsui et al. (2004)
	20	11-Oxo-7a-obacunol	Leaves	Mitsui et al. (2004)
	21	11β-Hydroxycneorin G	Leaves	Mitsui et al. (2004)
	22	11β-Oxocneorin G	Leaves	Mitsui et al. (2004)
	23	Cedrellin	Leaves	Luo et al. (2000)
	24	Toonins B	Roots	Dong et al. (2013a)
	25	Grandifoliolenone	Barks	Mitsui et al. (2007)
	26	Bourjotinolone A	Roots	Dong et al. (2013a)
	27	Toona triterpenoids A	Barks	Mitsui et al. (2007)
	28	Toona triterpenoids B	Barks	Mitsui et al. (2007)
	29	Piscidinol A	Barks	Mitsui et al. (2007)
	30	Hispidol B	Barks	Mitsui et al. (2007)
	31	20-Hydroxy-24-dammaren-3-one	Barks	Tang et al. (2016)
	32	(20*S*)-3-oxo-tirucalla-25-nor-7-en-24-oic acid	Barks	Tang et al. (2016)
	33	(20*S*)-5α,8α-epidioxy-3-oxo-24-nor-6.9(11)-dien-23-oic acid	Barks	Tang et al. (2016)
	34	Ocotillone	Barks	Tang et al. (2016)
	35	(20*S*,24*R*)-epoxydammarane-12.25-diol-3-one	Barks	Tang et al. (2016)
	36	(20*S*,24*R*)-epoxydammarane-3β,25-diolmarane-3β,25-diol	Barks	Tang et al. (2016)
	37	Methyl shoreate	Barks	Tang et al. (2016)
	38	Shoreic acid	Barks	Tang et al. (2016)
	39	Richenone	Barks	Tang et al. (2016)
	40	Cabralealactone	Barks	Tang et al. (2016)
	41	Cylindrictone D	Barks	Tang et al. (2016)
	42	Hollongdione	Barks	Tang et al. (2016)
	43	4,4,14-Trimethyl-3-oxo-24-nor-5α,13α,14*β*,17α,20S-chol-7-en-23-oic acid	Barks	Tang et al. (2016)
	44	(20*S*,24*S*)-dihydroxydammar-25-en-3-one	Barks	Tang et al. (2016)
	45	Bourjotinolone B	Barks	Tang et al. (2016)
	46	21α-Methylmeliandiol	Barks	Mitsui et al. (2007)
	47	21*β*-Methylmeliandiol	Barks	Mitsui et al. (2007)
	48	3-*O*-acetyl-21*R*-*O*-methyltoosendanpentol	Barks	Mitsui et al. (2007)
	49	3-*O*-acetyl-21S-*O*-methyltoosendanpentol	Barks	Mitsui et al. (2007)
	50	Sapellin E acetate	Barks	Mitsui et al. (2007)
	51	Azadirone	Barks	Mitsui et al. (2007)
	52	Toosendanin	Barks	Anonymous (1972)
	53	Phytol	Leaves	Luo et al. (2000)
	54	2,6,10-Phytatriene-1,14,15-triol	Leaves	Luo et al. (2000)
	55	(2*E*, 6*E*, 10*E*)-3,7,11,15-tetramethylhexadeca-2,6-10-triene-1, 14,15-triol	Fruits	Hou et al. (2011)
	56	Eudesm-4(15)-ene-1β,6α-diol	Fruits	Hou et al. (2011)
Phenylpropanoids	**57**	Cedralins A	Leaves	Lee et al. (2010)
	58	Cedralins B	Leaves	Lee et al. (2010)
	59	Toonins C	Root	Dong et al. (2013a)
	60	Matairesinol	Root	Dong et al. (2013a)
	61	Lyoniresinol	Root	Dong et al. (2013a)
	62	Scopoletin	Leaves	Luo et al. (2001) Shen et al. (2013)
	63	4, 7-Dimethoxy-5-methylcoumarin	Leaves	Shen et al. (2013)
	64	Ficusesquilignans A	Fruits	Hou et al. (2011)
	65	Ficusesquilignans B	Fruits	Hou et al. (2011)

Box 1 (*Continued*)

Classification	No.	Chemical component	Part of plant	References
Flavonoids	**66**	(+)-Catechin	Rachis	Park et al. (1996)
	67	(−)-Epicatechin	Rachis	Park et al. (1996)
	68	Procyanidin B3	Leaves	Kakumu et al. (2014)
			Stems	Zhao et al. (2009)
	69	Procyanidin B4	Stems	Zhao et al. (2009)
	70	Quercetin	Leaves	Zhang et al. (2001) Zhan and Zhang (2000)
	71	Quercitrin	Leaves	Zhang et al. (2001)
			Rachis	Park et al. (1996)
	72	Isoquercitrin	Rachis	Park et al. (1996)
			Bark	Li et al. (2006)
			Leaves	Zhang et al. (2001)
	73	Rutin	Rachis	Park et al. (1996)
	74	Kaempferol	Leaves	Luo et al. (2001)
	75	Kaempferol-3-*O*-α-l-rhamopyranoside	Fruits	Hou et al. (2011) Shen et al. (2013)
	76	Astragalin	Leaves	Shen et al. (2013)
	77	Myricetin	Bark	Li et al. (2006)
	78	Myricitrin	Bark	Li et al. (2006)
	79	Quercetin-3-*O*-(2″-*O*-galloyl)-*β*-d-glucopyranoside	Leaves	Cheng et al. (2009)
	80	Astragalin-2″-*O*-gallate	Leaves	Kakumu et al. (2014)
	81	Loropetalin D	Leaves	Kakumu et al. (2014)
	82	6,7,8,2′-Tetramethoxy-5,6′-dihydroxy-flavone	Leaves	Luo et al. (2001)
	83	5,7-Dihydroxy-8-methoxy flavone	Leaves	Luo et al. (2001)
Others	**84**	*bis*-(*p*-Hydroxyphenyl) ether	Rachis	Park et al. (1996)
	85	Gallic acid	Leaves	Chen et al. (2009b) Yang et al. (2013)
	86	Methyl gallate	Rachis	Park et al. (1996)
	87	Ethyl gallate	Leaves	Luo et al. (2001) Shen et al. (2013) [17]
	88	Syringic acid	Roots	Dong et al. (2013a)
	89	3,5-Dihydroxy-phenyl ether	Fruits	Hou et al. (2011)
	90	4-Methoxy-6-(2′,4′-dihydroxy-6′-methylphenyl)-pyran-2-one	Roots	Dong et al. (2013a)
	91	4-Hydroxy-3-methoxybenzene-ethanol	Roots	Dong et al. (2013a)
	92	3α-Hydroxy-5,6-epoxy-7-megastigmen-9-one	Leaves	Luo et al. (2001)
	93	Aloeemodin	Roots	Dong et al. (2013a)
	94	*β*-Sitosterol	Bark	Li et al. (2006) Dong et al. (2013a) Anonymous (1972)
	95	Daucosterol	Leaves	Yang et al. (2013)
	96	1,2,6-Tri-*O*-galloyl-*β*-d-glucopyranose	Leaves	Cheng et al. (2009)
	97	1,2,3,4,6-Penta-*O*-galloyl-*β*-d-glucopyranose	Leaves	Shen et al. (2013)
	98	1-*O*-methyl-2,3,4,6-tetra-*O*-galloyl-*β*-d-glucopyanose	Seeds	Zhao et al. (2011)
	99	(*S*,*S*)-γ-glutamyl-(*cis*-*S*-1-propenyl)thioglycine	Shoots	Li et al. (2013)
	100	(*S*,*S*)-γ-glutamyl-(*trans*-*S*-1-propenyl)thioglycine	Shoots	Li et al. (2013)
	101	γ-Glutamyl-(*cis*-*S*-1-propenyl)-cysteine	Shoots	Li et al. (2013)
	102	γ-Glutamyl-(*trans*-*S*-1-propenyl)-cysteine	Shoots	Li et al. (2013)
	103	*cis*-*S*-1-propenyl-l-cysteine	Shoots	Li et al. (2013)
	104	*trans*-*S*-1-Propenyl-l-cysteine	Shoots	Li et al. (2013)
	105	Adenosine	Rachis	Park et al. (1996)

(**37**), methyl shoreate (**38**), shoreic acid (**39**), richenone (**40**), cabralealactone (**41**), cylindrictone D (**42**), hollongdione (**43**), 4,4,14-trimethyl-3-*oxo*-24-nor-5α,13α,14β,17α,20*S*-chol-7-*en*-23-oic acid (**44**), (20*S*,24*S*)-dihydroxydammar-25-*en*-3-one (**45**), bourjotinolone B (**46**) (Tang et al., 2016), 21α-methylmeliandiol (**47**), 21β-methylmeliandiol (**48**), 3-*O*-acetyl-21*R*-*O*-methyltoosendanpentol (**49**), 3-*O*-acetyl-21*S*-*O*-methyltoosendanpentol (**50**), toona triterpenoids C, D, F, sapellin E acetate (**51**), azadirone (**52**) (Mitsui et al., 2007), and toosendanin (**1**) (Anonymous, 1972).

Furthermore, there are also other terpenoids reported in this *T. sinensis*, including phytol (**53**), 2,6,10-phytatriene-1,14,15-triol (Luo et al., 2000), (2*E*,6*E*,10*E*)-3,7,11,15-tetramethylhexadeca-2,6-10-triene-1,14,15-triol, eudesm-4(15)-*ene*-1β,6α-diol (**54**) (Hou et al., 2011).



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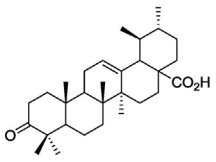

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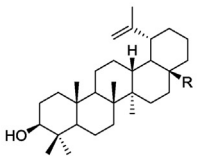

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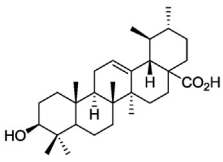

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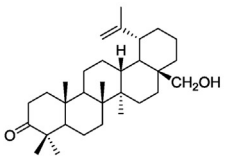

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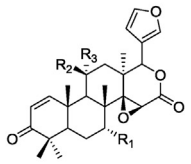

7 R_1=OAc; R_2=OH; R_3=H
8 R_1=OAc; R_2=H; R_3=OH
9 R_1=R_3=H; R_2=OH
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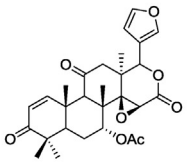
11 R_1=OAc; R_2=R_3=H
12 R_1=OH; R_2=R_3=H



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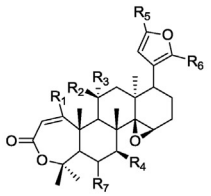

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17 R_1=R_2=R_3=R_4=R_5=R_6=H; R_7=Oac
18 R_1=R_4=OAc; R_2=R_3=R_5=R_7=H
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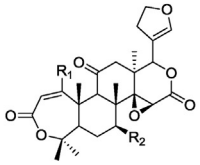

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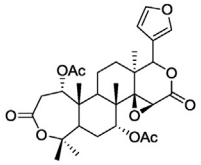

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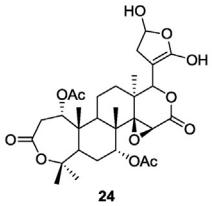

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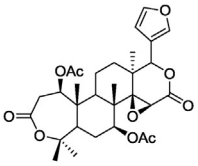

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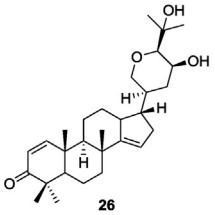

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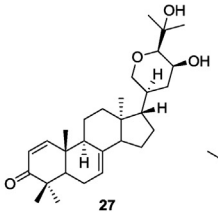

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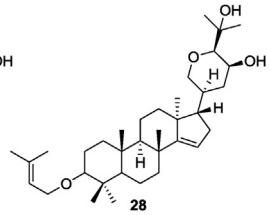

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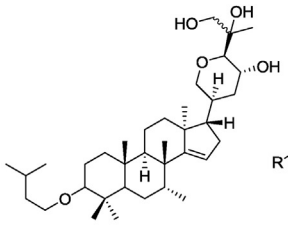

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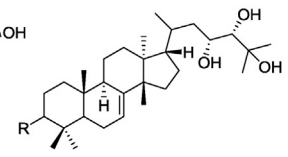
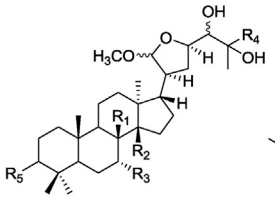
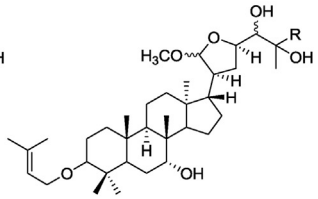


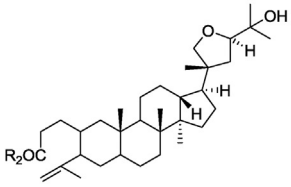
30 R=O
31 R=β-OH



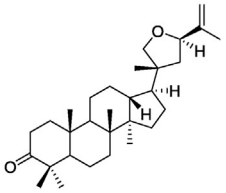
32 R_1=R_3=H; R_2=R_4=CH_3; R_5=O, 21*R*
33 R_1=R_3=H; R_2=R_4=CH_3; R_5=O, 21*S*
34 R_1=R_4=CH_3; R_2=H; R_3=OH; R_5=O, 21*R*
35 R_1=R_4=CH_3; R_2=H; R_3=OH; R_5=O, 21*S*



36 R=CH_3, 21*R*
37 R=CH_2OH, 21*S*



38 R=CH3
39 R=H



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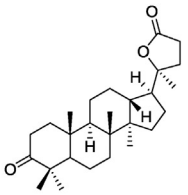

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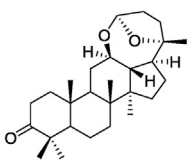

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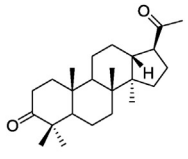

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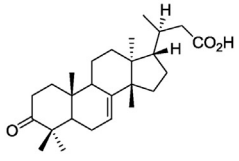

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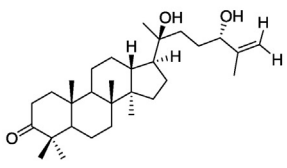

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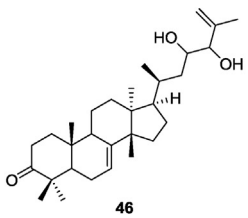

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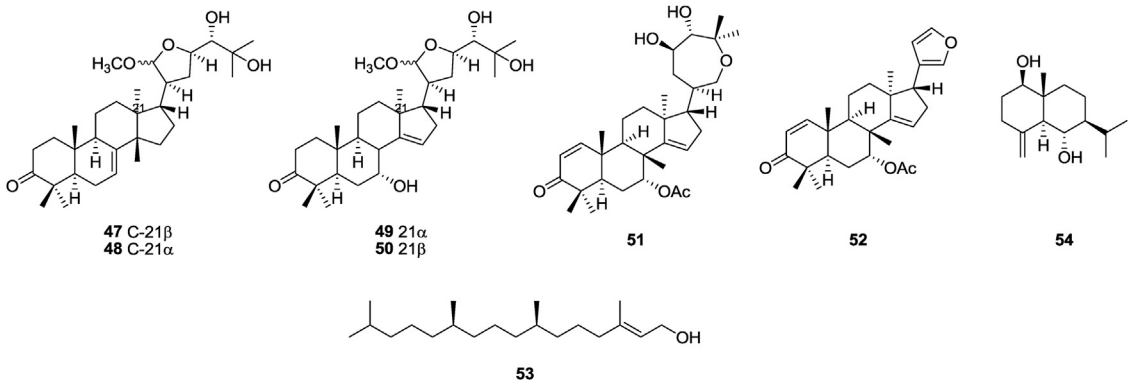


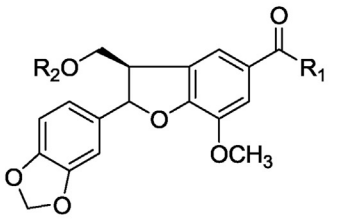
Phenylpropanoids

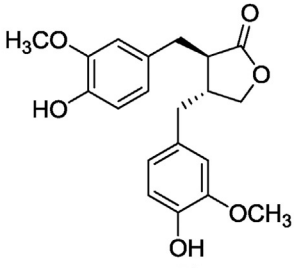
Phenylpropanoids, including lignins and coumarins, commonly exist in natural plants, and these compounds often have some interesting activities such as antiviral, antibacterial, anti-inflammatory and antitumor activities (de Souza et al., 2016; Hassan et al., 2016; Figueiredo et al., 2017).

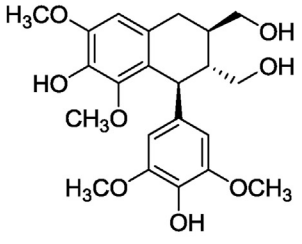
So far, nine phenylpropanoids have been found in the leaves, fruits and roots of *T. sinensis*, and these constituents were identified as cedralins A (**55**), B (**56**) (Lee et al., 2010), toonins C (**63**), matairesinol (**58**), lyoniresinol (**59**) (Dong et al., 2013a), scopoletin (**60**) (Luo et al., 2001), 4,7-dimethoxy-5-methylcoumarin (**61**) (Shen et al., 2013), and ficusesquilignans A (**62**), B (**63**) (Hou et al., 2011).

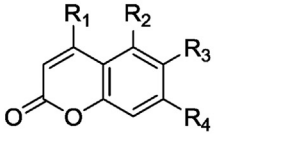
Flavonoids

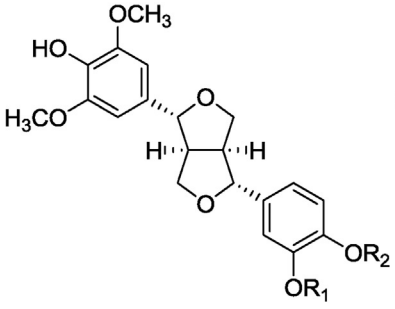
Flavonoids are common constituents in various plants all over the world. There were thirteen flavonoids in different parts of *T. sinensis* which were isolated and identified as (+)-catechin (**64**), (−)-epicatechin (**65**) (Park et al., 1996), procyanidin B3 (**66**) (Kakumu et al., 2014), procyanidin B4 (Zhao et al., 2009), quercetin, quercitrin (Zhang et al., 2001), isoquercitrin (**67**), rutin (Park et al., 1996), kaempferol (Luo et al., 2001), kaempferol-3-*O*-α-L-rhamopyranoside (**68**) (Hou et al., 2011), astragalin (**69**) (Shen et al., 2013), myricetin (**70**), myricitrin (**71**) (Li et al., 2006), quercetin-3-*O*-(2″-*O*-galloyl)-β-D-glucopyranoside (**72**) (Cheng et al., 2009),

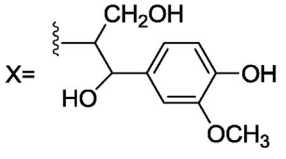




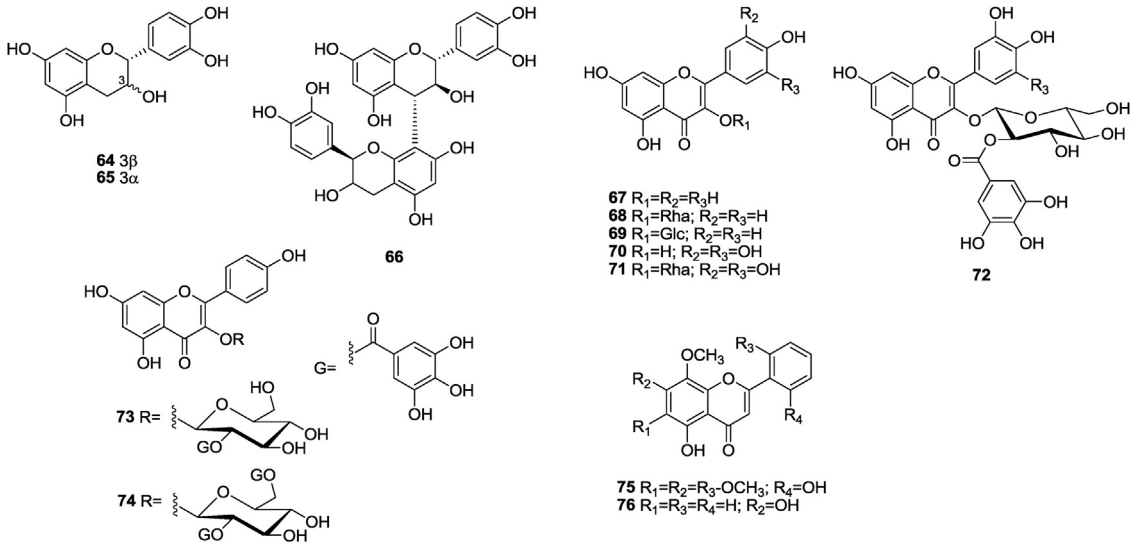






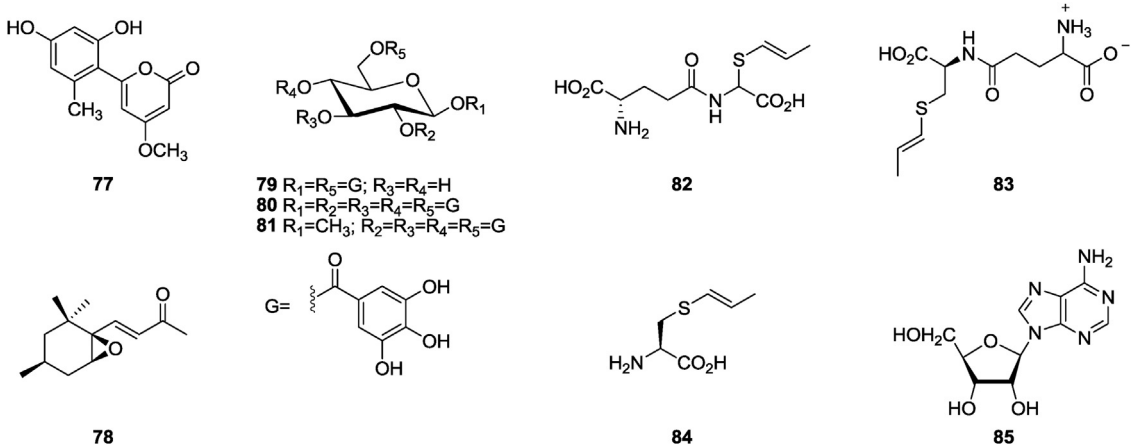


astragalin-2″-*O*-gallate (**73**), loropetalin D (**74**) (Kakumu et al., 2014), 6,7,8,2′-tetramethoxy-5,6′-dihydroxy-flavone (**75**), and 5,7-dihydroxy-8-methoxy flavone (**76**) (Luo et al., 2001).



Other compounds

Besides these compounds mentioned above, there are also other compounds, including phenols, sterols, anthraquinones, tannins, and sulfocompounds reported in *T. sinensis*. These constituents are identified as *bis*-(*p*-hydroxyphenyl) ether (Park et al., 1996), gallic acid (Chen et al., 2009), methyl gallate (Park et al., 1996), ethyl gallate (Luo et al., 2001), syringic acid (Dong et al., 2013a), 3,5-dihydroxy-phenylether (Hou et al., 2011), 4-methoxy-6-(2′,4′-dihydroxy-6′-methylphenyl)-pyran-2-one (**77**), 4-hydroxy-3-methoxybenzene-ethanol (Dong et al., 2013a), 3α-hydroxy-5, 6-epoxy-7-megastigmen-9-one (**78**) (Luo et al., 2001), aloeemodin (Dong et al., 2013a), β-sitosterol (Li et al., 2006), daucosterol (Yang et al., 2013), 1,2,6-*tri*-*O*-galloyl-β-D-glucopyranose (**79**) (Cheng et al., 2009), 1,2,3,4,6-penta-*O*-galloyl-β-D-glucopyranose (**80**) (Shen et al., 2013), (*S*,*S*)-γ-glutamyl-(*cis*-*S*-1-propenyl) thioglycine (**81**), (*S*,*S*)-γ-glutamyl-(*trans*-*S*-1-propenyl)thioglycine (**82**), γ-glutamyl-(*cis*-*S*-1-propenyl)-cysteine (**83**), γ-glutamyl-(*trans*-*S*-1-propenyl)-cysteine, *cis*-*S*-1-propenyl-L-cysteine (**84**), *trans*-*S*-1-propenyl-L-cysteine (Li et al., 2013), and adenosine (**85**) (Park et al., 1996).



Pharmacology

Previous investigations have comprehensively considered the pharmacological activities of *T. sinensis* and reported that this plant possesses various pharmacological activities including anti-tumor, hypoglycemic, antioxidant, anti-inflammatory, protecting effect on ischemia–reperfusion injury, hepatoprotective, antibacterial and antiviral, anti-gout effect, male reproductive system protection, and anticoagulation effects (Box 2).

Anti-tumor effect

Toona sinensis is a known TCM with the function of heat-clearing and detoxifying, and anti-tumor effects are important pharmacological activities of *T. sinensis* which have been comprehensively investigated, including leukemia, lung cancer, oral carcinoma, cervical carcinoma, osteosarcoma, ovarian cancer, prostate cancer, renal carcinoma, gastric cancer, colon cancer, and breast cancer (Hseu et al., 2011).

By using MTT assays *in vitro*, Chen et al. (2011a) found that ethyl acetate extracts of *T. sinensis* (ACTSL) significantly inhibited the proliferation of leukemia K562 cell line with the IC_{50} was 102.53 μg/ml. Later in 2012, it is reported that water extracts of *T. sinensis* (TSL) could arrest leukemia HL-60 cells at G1–S transition phase and down-regulate VEGF (Huang et al., 2012). In 2016, research of Yang et al. (2017) found that TSL (50 mg/kg) had

Box 2
The pharmacological activities of *Toona sinensis*.

Pharmacological effects	Detail	Tested substance	Doses/concentrations	References
Antitumor effect	Leukemia (K562 cell line)	ACTSL	IC_{50} was 102.53 μg/ml	Chen et al. (2011a)
	Leukemia (WEHI-3 cell line)	TSL	50 mg/kg on WEHI-3 cell bearing mice	Yang et al. (2017)
	Leukemia (HL-60 cell line)	TSL	10–75 μg/ml	Huang et al. (2012)
		Gallic acid	5, 10 μg/ml	Huang et al. (2012) Kakumu et al. (2014)
	Leukemia (HL-60 and K562 cell lines)	Cedralins A	IC_{50} were 26.2 and 22.4 μg/ml	Lee et al. (2010)
	Leukemia (HL-60 cell line)	Loropetalin D	50 μM	Kakumu et al. (2014)
		Quercetin		
		Quercitrin		
		Afzelin		
		Astragalin 2′′-*O*-gallate		
		(+)-Catechin		
	Lung cancer (H441, H520, H661 cell lines)	TSL	0.125–1.0 mg/ml for 24 or 48 h, IC_{50} were 1.2, 0.73 and 0.29 mg/ml for H441, H520 and H661 cells	Wang et al. (2010); Yang et al. (2010a,b)
	Oral carcinoma	TSL	1.0 g/kg	Wang et al. (2016)
		Gallic acid	250, 500 μg/ml	Chia et al. (2010)
	Gastric cancer (MGC-803 cell line)	Betulonic acid	IC_{50} was 17.7 μM	Yang et al. (2013)
		3-*Oxo*-12-*en*-28-oic acid	IC_{50} was 13.6 μM	
	Gastric cancer (SGC-7901 cell line)	ACTSL	IC_{50} was 168.47 μg/ml	Chen et al. (2011a)
	Prostatic cancer (DU145 cell line)	Gallic acid	25–100 μg/ml	Chen et al. (2009)
	Prostatic cancer (PC3 cell line)	Betulonic acid	IC_{50} was 26.5 μM	Yang et al. (2013)
		3-*Oxo*-12-*en*-28-oic acid	IC_{50} was 21.9 μM	
	Ovarian cancer (SKOV3 cell line)	TSL	0–1000 μg/ml	Chang et al. (2006)
	Cervical carcinoma (Hela cell line)	TSL	25, 50 μg/ml	Zhen et al. (2014)
	Renal carcinoma (ccRCC cell line)	TSL	–	Chen et al. (2016)
	Rsteosarcoma (Saos-2 cell line)	TSL	IC_{50} was 42.8–52.3 μg/ml *in vitro* 1 g/kg and 5 g/kg on Saos-2 cell bearing mice	Chen et al. (2017b)
	Colon cancer Caco-2 cell	TSL	IC_{50} was 4.0 μg/ml	Liu et al. (2012)
	Liver cancer HepG2 cell	TSL	IC_{50} was 153.16 μg/ml	
	Breast cancer MCF-7 cell	TSL	IC_{50} was 193.46 μg/ml	
Hypoglycemic effects	Glucose uptake-enhancing effect	ETSL	0.001, 0.01, 0.1 mg/ml, for 60 min	Yang et al. (2003)
	Inhibiting LDL glycation induced by glucose and glyoxal	TSL	0.5 mg/ml	Hsieh et al. (2005)
	Alleviating hyperglycemia *via* altering adipose glucose transporter 4	TSL	0.5, 1, 2 g/kg/14 days	Wang et al. (2008a)
	Hypoglcemic effects on diabetic mice	FTSL	0.6, 0.12 mg/kg	Zhang et al. (2008, 2011)
	Protective effects on hepatic injury at early stage in diabetic rats	TPST	60, 80, 100 mg/kg, for 14 days	Xing and Chen (2011)
	Hypoglycemic effect in diabetic rats	STSL	15 mg/kg, for 15 days	Du et al. (2011)
	kidney protecting effects in diabetic rats	STSL	50 mg/kg, for 10 weeks	Li et al. (2016)
	Preventing the progression of diabetes	NPTSL	12.5–100 μg/ml *in vitro*; 150 mg/kg for 8 weeks *in vivo*	Hsieh et al. (2012)
	Stimulating glucose uptake and ameliorating insulin resistance	ETSL	0, 10, 50, 70, and 95%	Liu et al. (2015)
	α-Glucosidase inhibitory activities	Gallic acid	IC_{50} was 24.3 μM	
		(+)-Catechin	IC_{50} was 190.7 μM	Zhao et al. (2009)
		(−)-Epicatechin	IC_{50} was 189.0 μM	
		Procyanidin B3	IC_{50} was 111.0 μM	
		Procyanidin B4	IC_{50} was 89.0 μM	
	Reducing the risk of diabetes and its secondary complications *via* reducing oxidative stress in the liver	Quercetin	200 mg/kg	Zhang et al. (2016)
Antioxidant effects	Against hydrogen peroxide-induced oxidative stress and DNA damage in MDCK cells	Methyl gallate	100 μM	Hsieh et al. (2004)
	In vitro antioxidant experiments	TSL	0.1–1.6 mg/ml	Zhang et al. (2007)
		TSL	25–100 μg/ml	Hseu et al. (2008)
		Gallic acid	50 μg/ml	
		TPST	-	Wang et al. (2008)

Box 2 (*Continued*)

Pharmacological effects	Detail	Tested substance	Doses/concentrations	References
	Antioxidant properties that protect endothelial cells from oxidative stress	TSL	50–100 μg/ml	Yang et al. (2011)
	Up-regulating antioxidant enzymes in SD rats	FETSL	0.5 and 1.0 mg/kg	Chen et al. (2013)
Anti-inflammatory effects	Inhibiting carrageenin-induced paw edema in rats	TSL	0.5 and 1.0 mg/kg (*p.o.*)	Ruan et al. (2010)
	Treating adjuvant-induced arthritis in rats	TPST	35 and 70 mg/kg (*p.o.*)	Yang and Chen (2012)
	Inhibiting LPS-induced inflammation in mice *via* suppressing NF-κB pathway	TSL Gallic acid	100 mg/kg (*p.o.*) 5 mg/kg (*p.o.*)	Hsiang et al. (2013)
	Inhibiting LPS-induced inflammation in vascular smooth muscle cells (A7r5 cell line) *via* suppressing NF-κB pathway	TSL Gallic acid	25–100 μg/ml 5 μg/ml	Yang et al. (2014)
	Inhibiting inflammatory responses in RAW264.7 cells *via* activating Keap1/Nrf2/HO-1 pathway	7-deacetylgedunin	1–25 μM	Chen et al. (2017a)
Protecting effects on ischemia–reperfusion	Protective effect on myocardial ischemia/reperfusion injury in rats	TPST	50, 100, 200 mg/kg/d (*p.o.*, for 7 days)	Li and Chen (2011a,b, 2012)
	protective effects on MODS caused by brain ischemia–reperfusion in rats	BUST	20,30 mg/kg/d (*p.o.*, for 7 days)	Yuan et al. (2013)
Hepatoprotective effect	Alleviating thioacetamide induced liver fibrosis	TSL	1 g/kg/d (*p.o.*, for 7 days)	Fan et al. (2007)
	Ameliorating antioxidant enzymes activity in H_2O_2 induced oxidative rats liver	TSL	0.013– 1.88 g/kg/d (*p.o.*, for 8 weeks)	Yu et al. (2012a)
	Protective effects on hepatic injury at early stage in diabetic rats	TPST	60, 80, 100 mg/kg (*p.o.*, for 14 days)	Xing and Chen (2011)
	Attenuating acetaminophen induced acute liver toxicity in HepG2 cells and mice *via* inducing antioxidant machinery and inhibiting inflammation	Quercitrin	25, 50 μg/ml; 10, 50 mg/kg/d (*p.o.*, for 7 days)	Truong et al. (2016)
Antiviral and antibacterial effects	Antiviral activity against SARS-CoV	TSL	IC_{50} = 30 μg/ml	Chen et al. (2008)
	Antiviral activity against H1N1	TSL	10–100 μg/ml	You et al. (2013)
	Antibacterial activity against *E. coli* C83902	TSL	MIC = 0.25 g/ml	Chen et al. (2011b)
	Antibacterial activity against *E. coli K88*	TSL	MIC = 0.125 g/ml	
	Antibacterial activity against *Salmonella* C500	TSL	MIC = 0.25 g/ml	
	Antibacterial activity against *Staphylococcus* CAU0183	TSL	MIC = 0.25 g/ml	
Anti-gout activity	Inhibiting XO	TSL	IC_{50} = 151.6 μg/ml	Liang et al. (2011)
	Inhibiting COX- 2	TSL	IC_{50} = 2.26 μg/ml	
	Hypouricemic effects on hyperuricemic mice	FTSL	50, 100, 200 mg/kg/d (*p.o.*, for 7 days)	Wang et al. (2011)
Male reproductive system protection	Suppressing steroidogenesis, cAMP-PKA pathway and steroidogenic enzymes activities in normal mouse leydig cells	TSL	0.005, 0.05, 0.5 mg/ml	Poon et al. (2005)
	TSL could improves the functions of sperm and testes	TSL	13 mg/kg/d (*p.o.*, for 8 weeks)	Yu et al. (2012a)
Anticoagulation effect	Anticoagulation effect of on adrenaline induced hypercoagulable rats *via* prolonging RT, APTT, TT and PT, and increasing AT-III activity	BUST	10, 20 mg/kg/d (*p.o.*, for 7 days)	Jin and Chen (2011)
	Enhancing fibrinolysis of topical FeCl3 induced carotid artery thrombosis rats *via* increasing t-PA, PL G and DD.	BUST	40 mg/kg/d (*p.o.*, for 7 days)	Jin and Chen (2011)
Other pharmacological effects	Lipolytic effect in differentiated 3T3-L1 adipocytes *via* protein kinase C pathway	TSL	0.001, 0.01, 0.1 mg/ml	Hsu et al. (2003)
	Suppressing BV-2 microglia mediated neuroinflammation	TSL	5, 10, 50 mg/ml	Wang et al. (2014a)
	Antinociceptive effect on acetic acid induced writhing in mice	TSL	0.003–1 g/kg (*p.o.*)	Su et al. (2015)
	Anticomplementary activity on complement-injured SH-SY5Y cells	1-*O*-methyl-2,3,4,6-tetra-O-galloyl-β-D-glucopyanose	100, 200 mg/ml	Zhao et al. (2011)
	Improving capacities of stress resistance and delaying senescence for *Caenorhabditis elegans*	FTSL	100 μg/ml	Yang et al. (2010)

ACTSL, ethyl acetate extracts of *T. sinensis* leaf; APTT, activated partial thromboplastin time; AT-III, increasing the activity of antithrombin III; BUST, n-butanol extract of the seeds of *T. sinensis*; CLP, cecal ligation and puncture; COX-2, cyclooxygenase-2; DD, D-dimer; FETSL, anaerobic fermented leaves extract of *T. sinensis*; ETSL, ethanol extracts of *T. sinensis* leaf; FTSL, total flavonoids of *T. sinensis* leaf; IC_{50}, half maximal inhibitory concentration; PLG, plasminogen; MODS, multiple organ dysfunction syndrome; ROS, reactive oxygen species; RT, cation time; STSL, water extracts of the seeds of *T. sinensis*; TSL, water extracts of *T. sinensis* leaf; t-PA, tissue plasminogen activator; TPST, total polyphenols from the seeds of *T. sinensis*; TT, thrombin time; PT, prothrombin time; XO, xanthine oxidase.

notable antitumor effect against leukemia in WEHI-3 cells bearing mice. Furthermore, it is reported that many interesting compounds isolated from the *T. sinensis* possess promising antitumor effects against leukemia, including cedralin A (**55**) (IC_{50} was 26.2 μg/ml), loropetalin D (**74**) (IC_{50} was 22.4 μg/ml) (Lee et al., 2010), quercetin, quercitrin, afzelin, astragalin 2″-*O*-gallate (**73**), (+)-catechin (**64**) (Kakumu et al., 2014) and gallic acid (Huang et al., 2012; Kakumu et al., 2014).

In 2010, using lung cancer cell lines including human lung adenocarcinoma H441 cell line, human lung squamous cell carcinoma H520 cell line, and human lung large cell carcinoma cell line H661, Wang et al. and Yang et al. reported that TSL possess notable antitumor potentials against lung cancer cell lines *via* cell cycle arrest and apoptosis, and the IC_{50} values were 1.2, 0.73 and 0.29 mg/ml for H441, H520 and H661 cells, respectively (Wang et al., 2010; Yang et al., 2010a,b).

In 2011, Chen et al. (2011) reported that ACTSL had the antitumor potential against gastric cancer SGC-7901 cell line with the IC_{50} value of 168.47 μg/ml. Later in 2013, Yang et al. (2013) reported betulonic acid (**5**) and 3-*oxo*-12-*en*-28-oic acid (**2**) isolated from *T. sinensis* inhibited the proliferation of gastric cancer MGC-803 (IC_{50} were 17.7 and 13.6 μM) and prostatic cancer PC3 cell lines (IC_{50} were 26.5 and 21.9 μM). Interestingly, gallic acid isolated from *T. sinensis* is also an important agent against prostatic cancer DU145 cells *via* inducing generation of reactive oxygen species (ROS) and mitochondria-mediated apoptosis; furthermore, gallic acid also showed a synergistic effect with doxorubicin in inhibiting DU145 cells' growth (Chen et al., 2009).

Water extracts of *T. sinensis* and gallic acid were also reported to be active agents against oral carcinoma *via* inducing apoptosis. Chang et al. (2006) reported that TSL induced apoptosis of human ovarian cancer SKOV3 cells and inhibits tumor growth in SKOV3 cells xenograft model. Zhen et al. (2014) found that TSL could induce cell cycle arrest in human cervical carcinoma HeLa cells *via* apoptosis. In 2016, it is reported that TSL inhibited the growth and migration of renal carcinoma ccRCC cells *via* inducing apoptosis (Chen et al., 2016). Recently, Chen et al. (2017b) revealed that TSL caused significant cytotoxicity in osteosarcoma Saos-2 cell *in vivo* and *in vitro via* inducing apoptosis (IC_{50} was 42.8–52.3 μg/ml *in vitro*, 1 g/kg and 5 g/kg on Saos-2 cell bearing mice).

Additionally, TSL was also reported to be an active agent against colon cancer Caco-2 cell, human liver cancer HepG2 cell and breast cancer MCF-7 cell lines, and the IC_{50} values were 4.0, 153.16 and 193.46 μg/ml, respectively (Liu et al., 2012).

Hypoglycemic effect

Currently, increasing researches have demonstrated that extracts/constituents from the *T. sinensis* have promising hypoglycemic potentials, which would be beneficial for the diabetes patients. In 2003, the research team of Yang et al. (2003) reported that ethanol extracts of *T. sinensis* leaf (ETSL) could enhance the cellular glucose uptake in basal and insulin stimulated 3T3-L1 adipocytes. In 2015, Liu et al. (2015) revealed that the mechanisms of TSL stimulating glucose uptake and ameliorating insulin resistance might be related to AMPK activation in skeletal muscles and up-regulation of PPARγ and normalized adiponectin in adipose tissues. In 2005, the inhibitory effect of TSL on LDL glycation induced by glucose and glyoxal was reported (Hsieh et al., 2005). It was also indicated that TSL could alleviate hyperglycemia *via* altering adipose glucose transporter 4 (Wang et al., 2008), and results of Zhang et al. (2008, 2011) indicated that total flavonoids of *T. sinensis* (FTSL) might be the active constituents corresponding to the hypoglycemic effects of this plant. Furthermore, it is reported that extracts of the seeds of *T. sinensis* (STSL) has hypoglycemic and kidney protecting effects in diabetic rats (Du et al., 2011; Li et al., 2016), and Xing and Chen found that total polyphenols from the seeds of *T. sinensis* (TPST) could inhibit hepatic injury at early stage in diabetic rats (Xing and Chen, 2011). In 2012, Hsieh et al. (2012) indicated the supercritical-CO_2 fluid extracted non-polar leaves extract of *T. sinensis* (NPTSL) could prevent the progression of type 2 diabetes. Besides, Zhao et al. (2009) reported that in this plant, gallic acid, (+)-catechin (**64**), (−)-epicatechin (**65**, and procyanidin B3 (**66**), and B4 showed α-glucosidase inhibitory activities with IC_{50} of 24.3, 190.7, 189.0, 111.0, and 89.0 μM, respectively. Zhang et al. (2016) indicated that quercetin is also an active agent in *T. sinensis* could reduce the risk of diabetes and its secondary complications *via* reducing oxidative stress in the liver.

Antioxidant effect

By using a series *in vitro* experiment, previous researches indicated that TSL and gallic acid are potential natural antioxidant agents (Zhang et al., 2007; Hseu et al., 2008; Cheng et al., 2009; Liu et al., 2012). In addition, Hsieh et al. (2004) reported the antioxidant effects of methyl gallate isolated from *T. sinensis* against hydrogen peroxide-induced oxidative stress and DNA damage in MDCK cells. In addition, the antioxidant effects of phenolic compounds in *T. sinensis* have been widely proved by using DPPH scavenging assays (Wang et al., 2008; Xing and Chen, 2010). In 2011, Yang et al. (2011) indicated that TSL could protect endothelial cells from oxidative stress which is beneficial for treating atherosclerosis. Later in 2013, another study reported the anaerobic fermented leaves extract of *T. sinensis* (FETSL) could up-regulate the expression of antioxidant enzymes in SD rats (Chen et al., 2013).

Anti-inflammatory effect

To date, natural derived anti-inflammatory agents play important and indispensable roles in preventing and treating inflammatory diseases (Wang et al., 2013). In addition, many natural products (including extracts and monomers) isolated form the *T. sinensis* have been reported to possess notable anti-inflammatory effects. Ruan et al. (2010) reported that TSL could inhibit the carrageenin- induced paw edema in rats *via* suppressing inflammatory mediators. Later in 2012, a report demonstrated that total polyphenols from the seeds of *T. sinensis* (TPST) had therapeutic effects on adjuvant-induced arthritis rats (Yang and Chen, 2012). Furthermore, using NF-κB transgenic mice and bioluminescence imaging, another two investigations revealed that TSL and gallic acid could inhibit LPS-induced inflammation *via* suppressing NF-κB pathway *in vivo* and *in vitro* (Hsiang et al., 2013; Yang et al., 2014). Recently, Chen et al. (2017) reported that the 7-deacetylgedunin (**13**) isolated form the *T. sinensis* suppresses LPS induced inflammatory responses in RAW264.7 cells through activating Keap1/Nrf2/HO-1 pathway.

Protecting effect on ischemia–reperfusion injury

Ischemia–reperfusion injury is one of the leading reasons for the death in the rescue and treatment of ischemic disease, in particularly the myocardial and brain tissues. In 2011, the protective effect of total polyphenols extracted from *T. sinensis* (TPST) on myocardial ischemia/reperfusion injury in rats were reported, and the possible mechanism might be correlated to decreasing creatine kinase (CK), cardiac troponin (cTn) I, malonaldehyde (MDA), thromboxane (TXB_2), whereas increasing superoxide dismutase (SOD) and 6-keto-PGF1 (Li and Chen, 2011a,b). Later in 2012, another paper by Li and Chen reported that the protective effect of TPST on myocardial ischemia/reperfusion injury is also related to alleviating inflammatory reactions *via* decreasing pro-inflammatory cytokines such as TNF-α & IL-6 and suppressing NF-κB pathway

(Li and Chen, 2012). Besides, Yuan et al. (2013) revealed that *n*-butanol extract of the seeds of *T. sinensis* (BUST) had protective effects on multiple organ dysfunction syndrome (MODS) caused by brain ischemia–reperfusion in rats *via* suppressing oxidative stress.

Hepatoprotective effect

Nowadays, increasing evidences have demonstrated that herbal medicines are good resources for finding hepatoprotective drugs. Interestingly, Fan et al. (2007) found that TSL could alleviate thioacetamide induced liver fibrosis *via* reducing TGFβR1 and collagen. In addition, another investigation in 2012 reported that TSL could ameliorate the antioxidant enzymes activity in H_2O_2 induced oxidative rats liver which would be beneficial for the hepatic detoxification (Yu et al., 2012). Recently, Truong et al. (2016) reported that the quercitrin extracted from the *T. sinensis* attenuated acetaminophen-induced acute liver toxicity in HepG2 Cells and mice, and the related mechanisms is correlated to activating defensive genes and inhibiting pro-inflammatory mediators *via* suppressing JNK and p38 pathway.

Antiviral and antibacterial effect

Currently, the antiviral and antibacterial effects of *T. sinensis* have aroused researchers' attention. In 2008, Chen et al. (2008) found that TSL had antiviral activity against SARS-CoV *in vitro* with an IC_{50} value of 30 μg/ml. Later in 2013, another report revealed that TSL could be used an alternative treatment and prophylaxis against H1N1 virus (You et al., 2013). Besides, it is reported that TSL also possessed promising antibacterial potential against *E. coli* C83902, *E. coli K88*, *Salmonella* C500, and *Staphylococcus* CAU0183, and the minimum inhibitory concentration (MIC) were 0.25, 0.125, 0.25 and 0.25 g/ml (Chen et al., 2011).

Anti-gout effect

Gout is a common painful diseases caused by accumulation of uric acid crystals in joints which is closely related to chronic purine metabolic disorder. In 2011, Liang et al. (2011) reported that TSL possessed significant inhibitory activities *in vitro* against xanthine oxidase (XO, IC_{50} was 151.6 μg/ml), cyclooxygenase (COX)-2 (IC_{50} was 2.26 μg/ml). In addition, Wang et al. (2011) reported the total flavonoids of *T. sinensis* leaf (FTSL) had notable hypouricemic effects on hyperuricemic mice *in vivo*. These results above indicate that *T. sinensis* possesses significant inhibitory effect on the progression of gout.

Male reproductive system protection

In 2005, results of Poon et al. (2005) suggested that TSL could increase the motility of sperms *via* suppressing steroidogenesis, cAMP-PKA pathway and steroidogenic enzymes activities in normal mouse leydig cells. Furthermore, another paper also reported TSL could improves the functions of sperm and testes *via* down-regulation of glutathione transferase mu6, heat shock protein 90 kDa-β, cofilin 2 and cyclophilin A, whereas up-regulation of crease3-hydroxy-3-methylglutaryl-coenzyme A synthase 2, heat shock glycoprotein 96, and pancreatic trypsin 1 (Yu et al., 2012b). These findings suggest *T. sinensis* is a valuable agent for men to ameliorate functions of sperm and testes under oxidative stress.

Anticoagulation effect

Using the topical $FeCl_3$ induced carotid artery thrombosis rats model, Liu and Chen (2009) reported that *n*-butanol extract of the seeds of *T. sinensis* (BUST) could obviously enhance the fibrinolysis of carotid artery thrombosis rats, and the main mechanism is involved in increasing tissue plasminogen activator (t-PA), plasminogen (PL G) and D-dimer (DD). Later in 2011, Jin and Chen (2011) reported that BUST had anticoagulation effect of on adrenaline induced hypercoagulable rats, which is might be correlated to prolonging the re-calcification time (RT), activated partial thromboplastin time (APTT), thrombin time (TT) and prothrombin time (PT), and increasing the activity of anti-thrombin III (AT-III).

Other pharmacological effects

Besides these pharmacological activities, it is also reported that TSL possesses lipolytic effect in differentiated 3T3-L1 adipocytes *via* protein kinase C pathway (Hsu et al., 2003), and Liu et al. (2014) reported that TSL could inhibit lipid accumulation through up-regulating genes related to lipolysis and fatty acid oxidation in adipocytes. Furthermore, it is reported that TSL could suppress BV-2 microglia mediated neuroinflammation (Wang et al., 2014), and have anti-nociceptive effect on acetic acid induced writhing in mice (Su et al., 2015). Besides, 1-*O*-methyl-2,3,4,6-tetra-*O*-galloyl-β-D-glucopyanose isolated from the *T. sinensis* had anti-complementary activity on complement-injured SH-SY5Y cells (Zhao et al., 2011), and FTSL could improve the capacities of stress resistance and delaying senescence for *Caenorhabditis elegans* (Yang et al., 2010).

Toxicology

T. sinensis is a plant could be used both as drug and food in China for thousands years. Generally, *T. sinensis* was commonly considered to be as a safe herbal drug, in particular the tender shoots of *T. sinensis* is delicious and nutritious food stuff. However, in some ancient books of TCM, such as the *Tang materia medica*, the bark of this plant is reported to be an herbal medicine with mild toxicity (Anonymous, 1999).

Currently, the systematic toxicity and safety evaluations of *T. sinensis* were still lacking, and only few reports had been documented. In 2007, Liao et al. (2007) evaluated the safety of the water extracts of *T. sinensis* leaf (TSL) using Ames test, and no obvious mutagenicity was found for all testing strains of *Salmonella typhimurium* TA98, TA100, TA102 and TA1535. In addition, Liao et al. (2007) also evaluated the acute oral toxicity of TSL (5000 mg/kg/day, for 14 days) and sub-acute oral toxicity of TSL (1000 mg/kg/day, for 28 days) in mice. The results indicated that TSL (5000 mg/kg/day, for 14 days) might decrease the food intake and kidney relative weight of female mice in acute oral toxicity test, and TSL (5000 mg/kg/day, for 28 days) could decrease the body weight gain, food intake and lung relative weight in sub-acute toxicity test. In another research, Liao et al. (2009) reported that no significant mutagenicity of water extract of fermented *T. sinensis* leaves (FTSL) was found in Ames test with the strains of *S. typhimurium* TA98, TA100, TA102 and TA1535; also, no obvious orally acute or subacute toxicity of FTSL (1000 mg/kg) was observed in mice. Moreover, the safety of a health care tea made by *T. sinensis* leaves was also evaluated on acute toxicity test in mice, ames test in *S. typhimurium*, micronucleus test of bone marrow PCE cell in mice, sperm shape abnormality test in mice, and the results revealed that no acute toxicity, genetic toxicity was observed (Cheng et al., 2007).

Conclusion

The present review provides a full-scale profile of the traditional usage, phytochemistry, pharmacology and toxicology of *T. sinensis*. In the present review, 109 compounds from different parts of this plant were summarized, and these compounds mainly concluded

terpenoids, phenylpropanoids, and flavonoids, *etc*. Additionally, the existing pharmacological investigations have revealed that agents or extracts from this plant have a wide spectrum of pharmacological effects which is beneficial for the health of human being, in particular for its anti-tumor and hypoglycemic activities. Emerging evidences from animal experiments and *in vitro* studies have demonstrated some traditional uses of *T. sinensis*; however, new drug development for this plant is still require lots of detailed studies in both the preclinical and clinical works.

Firstly, currently there are few systemically ADME (absorption, distribution, metabolism, and excretion) and toxicities data of the compounds/extracts derived from *T. sinensis*, which is an important reason for the delay of new drug development of this plant. Thus, more works should be done on the toxicities and pharmacokinetic profile of *T. sinensis*. Secondly, previous researches have reported various pharmacological effects of *T. sinensis*, however most of the researches only focused on the crude extract and gallic acid in this plant. Gallic acid have obvious biological activities, however, it's not a characteristic compound of *T. sinensis*. Due to this plant contains abundant terpenoids, extensive researches are required to investigate the pharmacological properties of monomers belonging to terpenoids in this plant. Third, as a traditional delicious food and nutritious food stuff, previous researches have revealed that this plant possesses good anti-tumor, hypoglycemic and antioxidant effects, the tender shoots and leaves of *T. sinensis* also have the huge potential for functional food development. Fourth, the *T. sinensis* was traditional used to treat dysentery, enteritis, carminative, itchiness, and eye infections in Chinese folk medicine. However, not all of these traditional uses above were demonstrated by current pharmacological experiments; thus, more possible medicinal potentials of this plant might be investigated in the future. Lastly, there is no clinic trial of this plant, thus more works should be devoted to do some systemic clinic trials for *T. sinensis* in the future.

In conclusion, this paper systemic reviewed the traditional usage, phytochemistry, pharmacology and toxicology of *T. sinensis*, which might highlight the importance of this plant and provides some directions for the future development of *T. sinensis*.

Authors' contributions

QWH and CJW contributed in conceiving this review; WP, YJL, MBH and MMZ contributed in collecting and analysis the references and data; JY and FL contributed in editing the manuscript; WP and YJL contributed in writing the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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