Constituents and Activities of *Acorus tatarinowii*

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Abstract

In this manuscript, chemical constituents, especially those with novel structures obtained from *Acorus tatarinowii* Schott (ATS), along with the pharmacological studies of those compounds, the volatile oil and the water soluble part of ATS, were reviewed.

Keywords: *Acorus tatarinowii*, Shichangpu

1. Introduction/Background

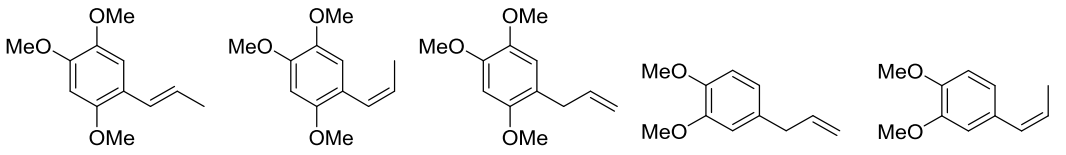
In traditional Chinese medicine Shichangpu, the most frequently appeared component in Chinese medicine formulas to treat neurological diseases such as Alzheimer's disease (Hu et al. 2012), is a famous resuscitation drug, exhibiting functions of expectorant, resuscitating, awakening and promoting intelligence. The source of Shichangpu should be *Acorus tatarinowii* Schott (Pharmacopoeia of People's Republic of China, 2010). But confused species such as *A. calamus* L. and *A. gramineus* Soland are also found in market. On the other hand, "nine sections changpu" which source is *Anemone altaica* Fisch, is a pseudo specie of Shichangpu. Numerous studies have been done on Shichangpu including the chemical constituents, *in vivo* and *in vitro* pharmacological activity, combination therapy with other medicines and so on. Herein, the chemical and pharmacological studies of *A. tatarinowii* Schott (ATS), the main source of Shichangpu were reviewed.

2. Chemical constituents of ATS

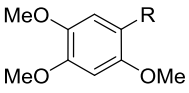
At the beginning of the 20th century, chemical and pharmacological studies of ATS were mainly focused on the volatile oil fractions. Volatile oil is believed to be the active component of Shichangpu as a resuscitation drug. Since 2010, many new compounds have been reported with the advanced separation technology and identification of compounds in ATS with LC-MS/MS became possible as well (Zhang et al. 2014).

2.1 Volatile oil & phenylpropanoids

The higher contents of the volatile oil of ATS are phenylpropanoids such as β-asarone (≈80%), α-asarone (≈4%), γ-asarone (syn. euasarone, ≈7%), methyleugenol (≈1%), *cis*-methylisoeugenol (≈3%), et al (Se et al. 2011), while the content of these compounds varies widely in different batches of herbs. By using GC-MS/MS, more and more volatile substances can be identified in ATS (Wang et al. 2012).

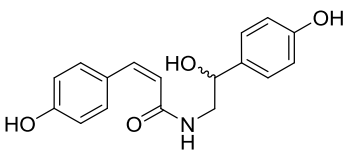


As a main class of secondary metabolites in ATS, a variety of phenylpropanoids had been reported. However, due to the relative simplicity of the structure, few derivatives with novel structure were reported. In 2000, Hu et al reported four compounds named respectively as isoacoramone, *cis*-epoxyasarone, (*threo*)1',2'-dihydroxyasarone and (*erythro*)1',2'-dihydroxyasarone in which isoacoramone and *cis*-epoxyasarone were obtained as a mixture (Hu et al. 2000).

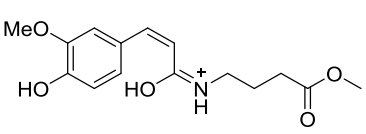


Isoacoramone R=-$COCH_2CH_3$
cis-Epoxyasarone R=1',2'-epoxypropane (*cis*)
(*threo*) 1',2'-Dihydroxyasarone R=-CH(OH)-CH(OH)-CH_3 (*threo*)
(*erythro*) 1',2'-Dihydroxyasarone R=-CH(OH)-CH(OH)-CH_3 (*erythro*)

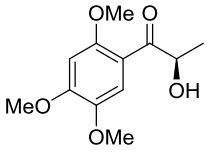
Tataramide A was reported as an amide of substituted *cis*-3-phenylacrylic acid (Wang et al. 1997). And another two novel amides of substituted *cis*- and *trans*-3-phenylacrylic acid were reported in 2015 without trivial names (Liang et al. 2015). Also, a new derivative of 2-methyl-3-phenyloxirane (2,4,5-trimethoxyl-2'-butoxy-1,2-phenylpropandiol) was reported by Zhu et al, with undefined configuration of the chiral carbons (Zhu et al. 2012). Tatarinoids A and B are novel phenylpropanoids with simple structure which are considered to be in equilibrium with each other *via* enediol intermediates (Tong et al. 2010).



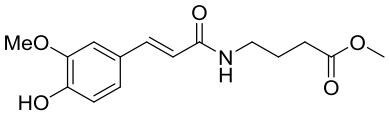
Tataramide A



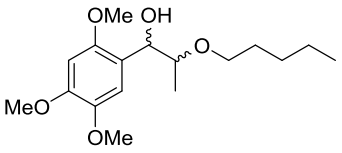
methyl (Z)-4-(3-(4-hydroxy-3-methoxy phenyl)acrylamido)butanoate enol isomer



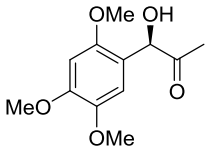
Tatarinoid A



methyl (*E*)-4-(3-(4-hydroxy-3-methoxyphenyl)acrylamido)butanoate



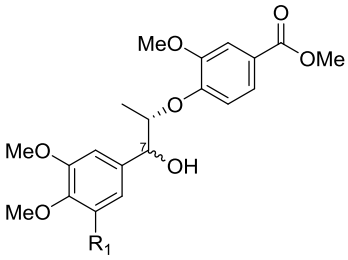
2,4,5-trimethoxyl-2'-butoxy-1,2-phenylpropan-diol



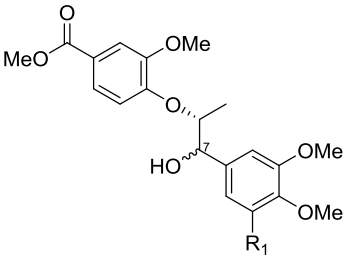
Tatarinoid B

2.2 Lignans

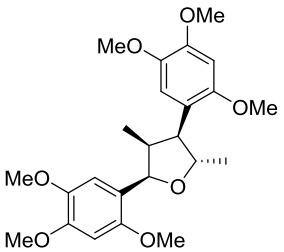
In recent years, devised new lignans with new skeletons were reported by different groups. Many lignans were isolated and reported with their enantiomers such as (±)-acortatarinowins A~C being reported as pairs of new 8-*O*-4'-type dinorneolignan enantiomers, (±)-acortatarinowins D and E as pairs of new 8-*O*-4'-type and rare C7-C8'-type neolignan enantiomers and (±)-acortatarinowin F as a pair of new bisepoxylignan enantiomers obtained along with known compounds (±)-eudesmin (Lu et al. 2015). Lu's group also reported other pairs of enantiomers such as (±)-acortatarinowins G~I in which (±)-acortatarinowin G were rare 7,8'-epoxy-8,7'-oxyneolignane (Lu et al. 2016). Recently, Qin's group reported identification of (±)-asarolignans B and C, which were the first examples of naturally occurring 7-*O*-7'-type neolignans, along with another new lignan enantiomers (±)-asarolignan G (Qin et al. 2017).



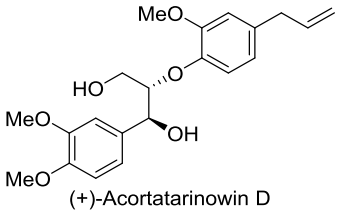
(+)-Acortatarinowin A R1=H, 7*S*
(-)-Acortatarinowin B R1=H, 7*R*
(+)-Acortatarinowin C R1=OMe, 7*S*



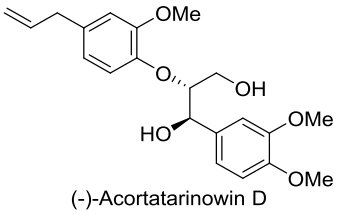
(-)-Acortatarinowin A R1=H, 7*R*
(+)-Acortatarinowin B R1=H, 7*S*
(-)-Acortatarinowin C R1=OMe, 7*R*



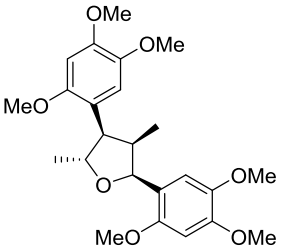
(+)-Acortatarinowin E



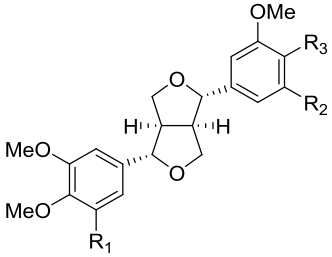
(+)-Acortatarinowin D



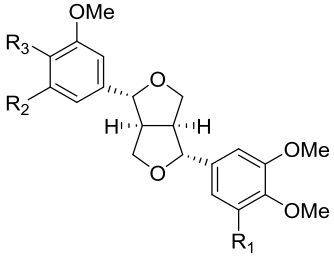
(-)-Acortatarinowin D



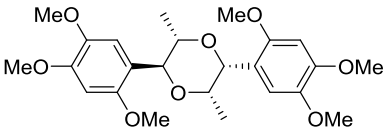
(-)-Acortatarinowin E



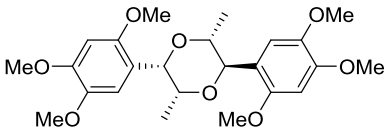
(+)-Acortatarinowin F R_1=R_2=OMe, R_3=H
(+)-Eudesmin R_1=R_2=H, R_3=OMe



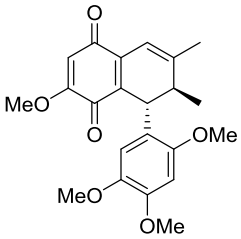
(-)-Acortatarinowin F R_1=R_2=OMe, R_3=H
(-)-Eudesmin R_1=R_2=H, R_3=OMe



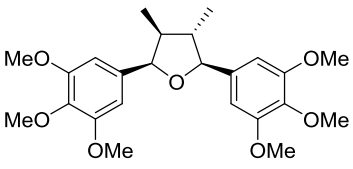
(+)-Acortatarinowin G



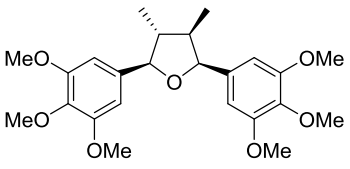
(-)-Acortatarinowin G



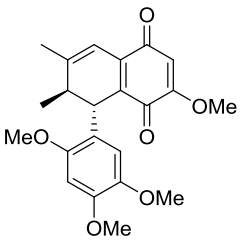
(+)-Acortatarinowin H



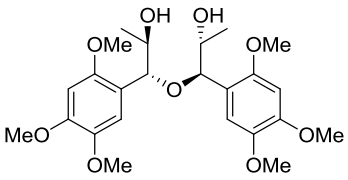
(+)-Acortatarinowin I

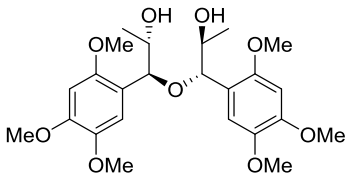


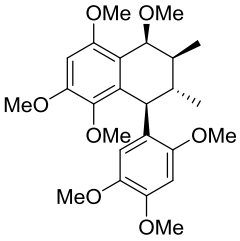
(-)-Acortatarinowin I

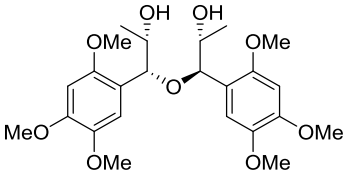


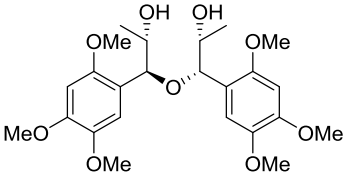
(-)-Acortatarinowin H

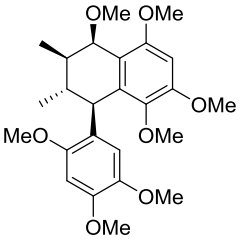

(+)-Asarolignan B


(-)-Asarolignan B

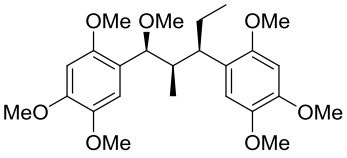

(+)-Asarolignan G

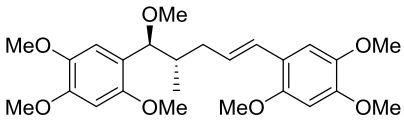

(+)-Asarolignan C

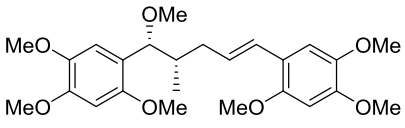

(-)-Asarolignan C

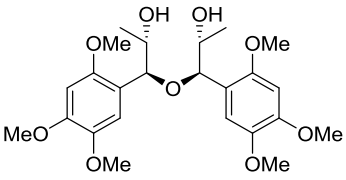

(-)-Asarolignan G

Lignans were also obtained as racemic mixtures or a mesomer in some cases, such as (±)-asarolignans D~F as racemates (Qin et al. 2017) and *meso*-asarolignan A as a mesomer.

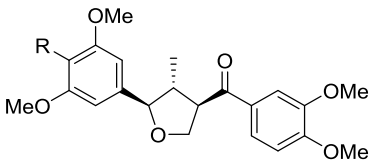

(±)-Asarolignan D

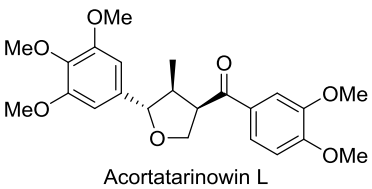

(±)-Asarolignan E

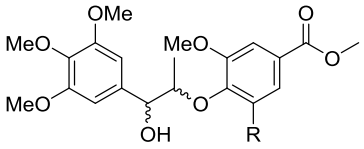

(±)-Asarolignan F


meso-Asarolignan A

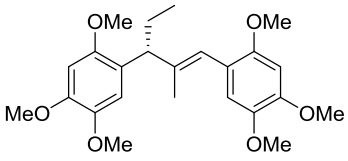
Tetrahydrofurans of 7-*O*-9'-type were also reported such as acortatarinowins J~L along with acortatarinowins M and N (Lu et al. 2016). Tatarinan S is a C8-C9'-type neolignan, which was naturally obtained for the first time in 2016 (Luo et al. 2016). New lignanamides were also reported such as tataramide B, tatarine E and acorusin A (Wang et al. 1997, Feng et al. 2016, Luo et al. 2016).


Acortatarinowin J R=OMe
Acortatarinowin K R=H

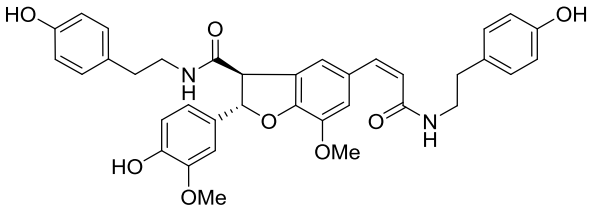

Acortatarinowin L



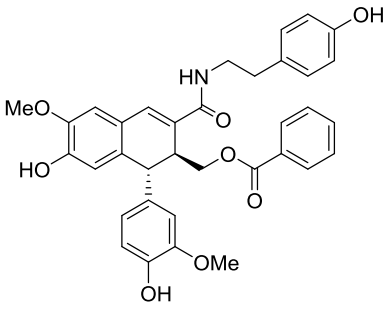
Acortatarinowin M R=OMe 7*S*,8*R*
Acortatarinowin N R=H 7*R*,8*S*



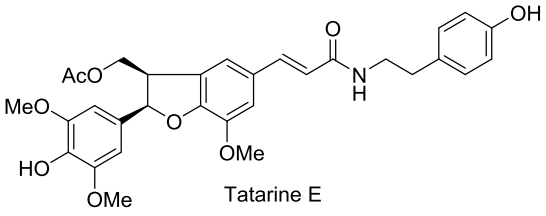
Tatarinan S



Tataramide B

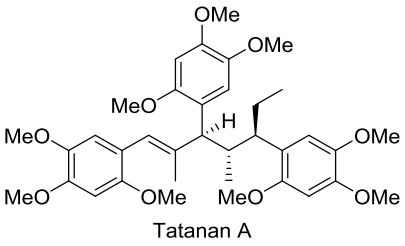


Acorusin A

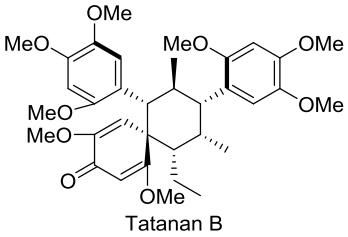


Tatarine E

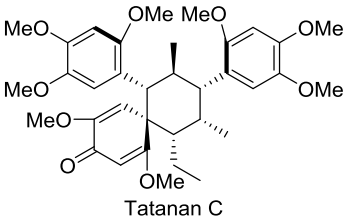
Oligomeric lignans also present in ATS. Tatanans A, B and C are novel sesquinlignans (Ni et al. 2011), while tatarinan T is dimeric lignan with the rare C8-C7' linkage pattern (Luo et al. 2016).



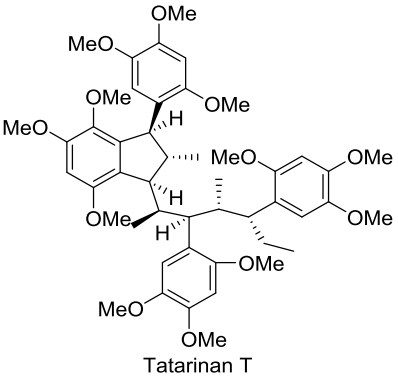
Tatanan A



Tatanan B

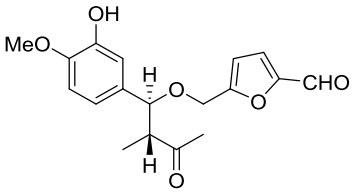


Tatanan C

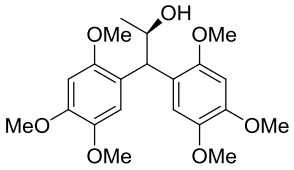


Tatarinan T

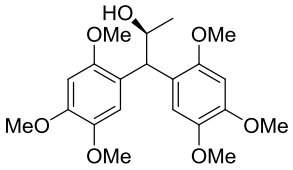
Besides normal lignans, some norlignans have been reported as well. Acorusin B is an unusual hybrid-norlignan derivative with 5-hydroxymethyl-2-furaldehyde moiety (Ni et al. 2016). (-)-Tatarinoid C was a rare trinorlignan firstly reported in 2010 (Tong et al. 2010), and enantiomers of which were then separated by chiral HPLC in 2017 (Qin et al. 2017). Another novel norlignan without trivial name was reported in 2015 (Liang et al. 2015).



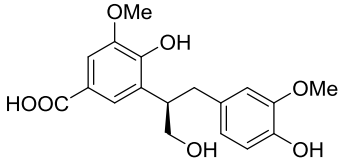
Acorusin B



(-)-Tatarinoid C



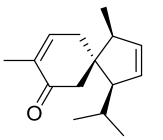
(+)-Tatarinoid C



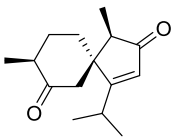
(*R*)-4-hydroxy-3-(1-hydroxy-3-(4-hydroxy-3-methoxyphenyl)propan-2-yl)-5-methoxybenzoic acid

2.3. Sesquiterpenoids

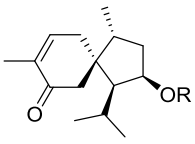
Skeletons of sesquiterpenoids in ATS are not abundant. Novel sesquiterpenoids mainly have three types of skeleton. New acorane-type sesquiterpenoids include tatanone A (Ni et al. 2013), acorusin D (Ni et al. 2016), 4-*Epi*-2-Hydroxyacorenone, 4-*epi*-2-acetoxyacorenone, acotatarone A and acotatarone B (Feng et al. 2014). Acorusin E, 1-hydroxy-7(11),9-guaiadien-8-one and acotatarone C are novel guaiane-type sesquiterpenoids (Feng et al. 2014, Ni et al. 2016, Zhu et al. 2010). New cadinane-type sesquiterpenoids tatarinowins A and B were reported in 2010 (Tong et al. 2010). Tatarinowin C is the 1,10-diol derivative of tatarinowin B obtained with acotatarone C (Feng et al. 2014). There may also be other stereoisomers and derivatives of tatarinowins A and B in ATS. Tatarinolacton is a novel sesquiterpene with an unprecedented epoxy lactone skeleton (Liang et al. 2015).



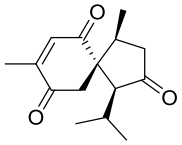
Tatanone A



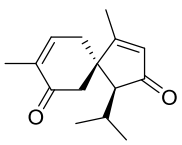
Acorusin D



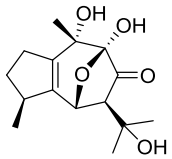
4-*epi*-2-Hydroxyacorenone R=H
4-*epi*-2-acetoxyacorenone R=Ac

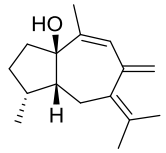


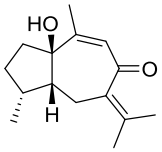
Acotatarone A

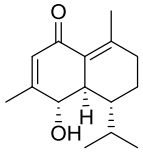


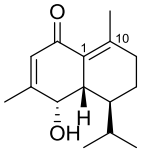
Acotatarone B

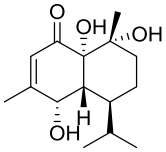

Acorusin E

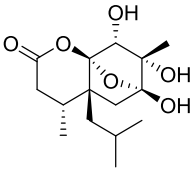

1-hydroxy-7(11),9-guaiadien-8-one

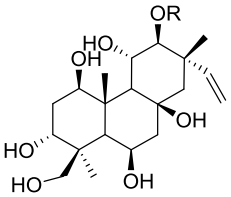

Acotatarone C


Tatarinowin A


Tatarinowin B


Tatarinowin C


Tatarinolacton

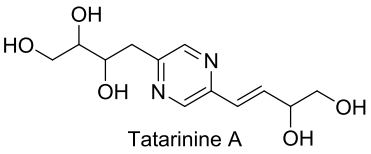

Tatarol R=H
Tataroside R=β-D-glc

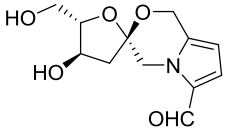
2.4 Diterpenoids

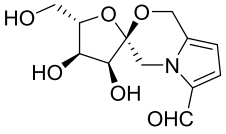
Abietane diterpenoid named as tatarol and its glucoside are the only two novel diterpenoids reported in the 1990s (Wang et al. 1997).

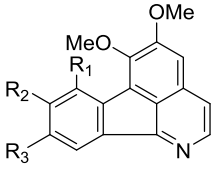
2.5 Alkaloids

Few novel alkaloids were reported besides the amides of phenylpropanoids. Tatarinine A is a pyrazine derivative with five hydroxyl groups (Tong et al. 2010a). Acortatarins A and B were novel spiroalkaloids with naturally unusual morpholine motif reported by Tong's group in the same year (Tong et al. 2010b). Novel azafluoranthene alkaloid named as tatarine D was isolated from ATS with two known alkaloids tatarine A and telitoxine (Feng et al. 2016).

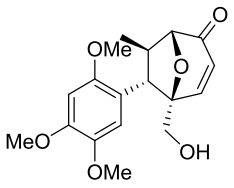

Tatarinine A


Acortatarin A


Acortatarin B



Tatarine A R_1=OH, R_2=H, R_3=H
Tatarine D R_1=H, R_2=OH, R_3=H
Telitoxine R_1=H, R_2=H, R_3=OH


Acorusin C

2.6 Anthraquinones, flavonoids, coumarins and triterpenoids

Known anthraquinones chrysophanol, physcion and emodin have been isolated from ATS (Zhu et al. 2010). Rhoifolin, astragalin, bergapten and other flavonoids, coumarins and triterpenoids such as cycloartenol, lupeol were also obtained (Tong et al. 2011). But none new anthraquinone, flavonoid, coumarin or triterpenoid was reported.

2.7 Miscellaneous

5-Hydroxymethyl-2-furaldehyde and its derivatives, glucoside of benzyl alcohol were often obtained from ATS (Ni et al. 2013). Acorusin C, which is a rare novel cycloheptenone oxide derivative was also identified (Ni et al. 2016).

3. Pharmacological Study of ATS

The rhizomes of ATS has been historically used to treat neurodegenerative diseases in China for thousands of years. In recent decades, *in vivo* and clinical pharmacological behaviors of Shichangpu have been widely studied. For example, in 2003 Sun's group reported a Chinese herbs formula which composed by Shichanpu, Gouqi and other seven herbs had great effects on improving the memory and cognitive function of AD-like animal model (Sun et al 2003). In the latest study Shichangpu showed an antidepressant effect on rat models by intragastric administration, and the mechanism of action (MOA) was supposed to be through upregulating motor, Akt, p70S6K or elF-4E protein expressions in the hippocampus (Wang et al 2016). However most pharmacological studies are based on the extract of ATS instead of the medicine.

3.1 Activities of the volatile oil

The volatile oil is considered to be the main active part of the ATS. So the pharmacological studies of ATS extract were mainly focused on the volatile oil in the past. It was used clinically for the treatment of unconsciousness such as pulmonary encephalopathy coma (Mao 2016). It was also been reported to have sedative, anticonvulsant activities *in vivo* and so on. Wu's group reported the volatile oil of ATS as well as β-asarone could significantly decrease the levels of blood cholesterol in atherosclerosis rat model and improve the blood rheological properties in hyperviscocity rats, while decrease ET level, and increase the NO content to reduce the degree of ischemic myocardial necrosis in myocardial ischemia rats, suggesting that the volatile oil and β-asarone had an important role of protecting the cardiovascular system (Wu et al. 2005). Hu's group reported that ATS volatile oil could increase the permeability of blood-brain barrier (BBB) (Hu et al, 2009), and β-asarone, α-asarone, *cis*-methylisoeugenol were confirmed to pass through the BBB along with the significant effects on a variety of learning and memory impairment models (Wu et al 2004). The volatile oil of ATS could also significantly improve the rat cortex convulsion threshold by the electrical stimulation which lasted longer than the positive control magnesium valproate with weaker effect. On the other hand, the expression of protein kinase C (PKC) was regulated by the volatile oil leading to reduction of nerve cell apoptosis, which was believed to be its MOA of the antiepileptic effect of the ATS volatile oil (Wang et al. 2015).

With macroporous resin, Zhou's group prepared different fractions of ATS to study the antidepressant effect of ATS extractions. The result showed only the fractions with abundant asarones were active (Zhou et al. 2015). α-Asarone and β-asarone are two main components of the ATS volatile oil, which caused thorough studies of these two compounds and are the most detailed. Reviews on asarones showed α- and

β-asarone could influence the nervous system, cardiovascular system, respiratory system and so on (Lan et al. 2013). Effect of combination of β-sarone and eugenol against PC12 cell injury induced by amyloid bata protein ($A\beta_{25-35}$) was also reported (Jiang et al 2006). Another research revealed that the anticonvulsant and sedative ingredient in ATS was eudesmin (Liu et al. 2015). Due to the fact that eudesmin is not a unique constituent of ATS, these results cannot explain the pharmacological activity of ATS comprehensively.

3.2 Activities of the water soluble part

In recent years, there were more researches on the activity of water soluble parts of ATS. Zhu's group revealed that the water extract of ATS could inhibit the exercise induced synthesis of 5-HT and TPH2 expression and prevent the exercise-induced decrease of 5-HT1B expression in the dorsal raphe of exercised rats (Zhu et al. 2014). *In vitro* activity study showed the hot water extract of ATS protected the differentiated PC12 cells against Aβ induced toxicity by inhibiting the mitochondrial apoptotic pathway and reducing ROS generation (An et al. 2014). Cai's group revealed that the main components of the water decoction of ATS were β-asarone (≈46%), 5-hydroxymethyl-2-furaldehyde (33%), et al (Cai et al. 2015). So it is not possible to determine whether the pharmacological activity of the water extract is attributable to asarone or other water-soluble compounds.

3.3 Activities of the novel compounds from ATS

In order to find the lead compounds for drug discovery and development, novel compounds were reported frequently with various activities. Alkaloid acortatarins A could inhibit high-glucose-induced ROD generation in mesangial cells by almost 50% at the concentration of 10μM (Tong et al. 2010c). Alkaloids tatarines A and D inhibited $A\beta_{42}$ aggregation with IC_{50} values of 45.0 and 26.0 μM, respectively, while the IC_{50} values of positive control epigallocatechin gallate (EGCG) were only 0.71 μM (Feng et al. 2016).

Among the novel lignan enantiomers acortatarinowins A~F, (+)-acortatarinowin A, (+)-acortatarinowin C and (-)-acortatarinowin F showed weak inhibitory activities against NO production in activated macrophages with IC_{50} values ranging from 23.3 to 29.5 μM. And IC_{50} values of positive control dexamethasone were 0.8μM. More interestingly, in that study (-)-acortatarinowin F showed inhibitory effect, while (+)-acortatarinowin F was inactive (Lu et al. 2015). Among acortatarinowins G~N only acortatarinowin L showed antioxidant activity using DPPH reducing antioxidant power assay with IC_{50} value of 16.4±0.22μg/mL, while the IC_{50} value of positive control trolox was 3.895±0.38μg/mL (Lu et al. 2016). Some lignans and phenylpropanoids were evaluated for anti-neuroinflammatory activities on TNF-α production in LPS-activated BV-2 cells. Asarolignan G, tatarinoid C and (7*R**,8*S**),-7,8-dihydroxy-asarone exhibited obvious inhibitory effects on the release of TNF-α at a concentration of 50 μM, suggesting the configuration was not critical to the antineuroinflammation activity in that case (Qin et al. 2017). Tatarinans T and S delayed the Aβ-induced paralysis in CL4176 transgenic *C. elegans* model at concentration

of 100μM, in which tatarinan S exhibited the higher protective effect, with its PT_{50} was 62.3% at 100μM and 30.8% at 10μM, respectively (Luo et al. 2016). Tatanans A~C displayed potent and selective *in vitro* GK activity higher than positive control GKA22 (Ni et al. 2011).

To identify the antidepressant compounds from ATS, assay for testing serotonin transporter (SERT) function was employed. Tatarinolactone significantly inhibited SERT activity (Liang at al. 2015). *In vitro* cytotoxicity of acorusins B, C, E and paeoniflorigenone against NCI-H1650, HepG2, BGC 823, HCT-116 and MCF-7 cell line exhibited moderate activities with IC_{50} values of 2.11~9.23 μM (Ni et al. 2016).

4. Conclusion

In the secondary metabolite research of ATS, lignans presents the highest probability of novel-compound occurrence. The high content of volatile oil in ATS caused the low contents of other kinds of compounds. So it is difficult to accumulate enough amounts of novel compounds for *in vivo* studies. On the other hand, lignans may have different levels of cytotoxicity, so it is difficult to carry out *in vivo* studies for *in vitro* active compounds without structural modification.

In the study of pharmacological activities of ATS, the volatile oil portion is still the most striking part. Although β-asarone is easy to pass through the BBB, with many experimental evidence indicating it is the active ingredient for the activities of ATS on the nervous system, it has the possibility to be carcinogenic, teratogenic and mutagenic. As a result, it is impossible to develop β-asarone alone to be a drug. In fact, volatile compounds of traditional Chinese medicine lose a lot in the boiling process. The actual amount of asarones into the human body is much lower than the content in the herbs. On the other hand, besides β-asarone, other volatile compounds in Shichangpu are also bioactive. Then, combination of β-asarone and other compounds may be promising research direction in the future.

From the existing literature, the *in vivo* study of ATS and the chemical research is often reported separately. So the chemical substance for treating nervous system disease of ATS has still not been fully confirmed. Many studies have shown that traditional Chinese medicine has the characteristics of multi-targeting, and interaction of multi-active substances. Therefore, the combination of active research and chemical composition analysis with statistical help such as partial least squares (PLS) may be helpful for clarifying the active ingredients of ATS. Then the quality standards of Shichangpu will be more accurate, and it will be easier to distinguish between its confused species and pseudo species.

Acknowledgments

The authors are grateful to the National Natural Science Foundation of China (81402775) and the grants from Shanghai Municipal Education Commission (12YZ054).

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