REVIEW

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Stilbene glucoside: recent advances in pharmacology, bioinformatics investigation, toxicity and future opportunities

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Background: 2,3,5,4'-Tetrahydroxystilbene-2-*O*-β-D-glucoside (TSG) from *Polygonum multijiorum* Thunb. (PMT), is a major bioactive component. This review is aimed to summarize the present development of TSG regarding pharmaceutics, pharmacology and toxicology, with a focus on the novel mechanism of drug-induced toxicity and provides insight for its potential developments and applications in the future on traditional Chinese medicine. *Methods*: Studies about TSG's activities and toxicity were searched and summarized. Targets and mechanisms were predicted and analyzed with network pharmacology methods. Affinities and binding modes of key targets with TSG were verified by AutoDock Vina software. *Results*: TSG plays an essential role among the chemical components of PMT because of multiple pharmacological activities, which suggests a potential application of TSG for a variety of diseases, like atherosclerosis, Alzheimer's disease, Parkinson's disease, cerebral I/R injury, diabetes, osteoporosis, colitis. However, mild liver toxicity of TSG is also pointed out. *Conclusions*: As a biologically active natural product in PMT, TSG has shown prospective pharmacological activities, particularly as an agent for cardiovascular protection and neuroprotection.

1. Introduction

As a widely used traditional Chinese medicine (TCM), *Polygonum multijiorum* Thunb. (PMT, Fig. 1) was first recorded in Rihuazi Bencao (a monograph about TCM). Dry root of PMT is described in the Chinese Pharmacopoeia and has been clinically used for more than 1000 years for many diseases, such as aging, hyperlipidemic, inflammation, liver protection, atherosclerosis, tumor. PMT is frequently used with the combination of other Chinese herbs, including *Angelica sinensis* (Oliv.) Diels (当归), *Astragalus membranaceus* (Fisch.) Bunge. (黄芪), *Panax ginseng* C. A. Mey (人参), *Poria cocos* (Schw.) Wolf (茯苓), and so on (Zhang et al. 2019). Clinically, nearly 300 patented TCMs containing or made from PMT are available from the Chinese market and in some other Asian countries, 61 of which are collected in Chinese Pharmacopoeia, e.g. Anshenbunao liquid, Shouwu pill, Xuezhiling tablet, Yi Shen Wu Fa Oral Liquid and Yangxue Shengfa capsule (Yin et al. 2016).

The structure of 2,3,5,4'-tetrahydroxystilbene-2-*O*-β-D-glucoside (stilbene glucoside, TSG, Fig. 2), was first extracted and isolated from PMT in 1975 (Heta et al. 1975). More than 90% TSG in PMT is trans-form. It was reported that TSG contributed markedly to resisting caducity, alleviating constipation, reducing serum lipids, protecting nerves, protecting liver, antitumor activity, etc. However, one has to pay special attention to adverse effects.

In this review, we focus on references of pharmacology and toxicity of TSG that have been published up to now for providing a comprehensive understanding. Network pharmacology, a new method for drug research with databases and software (Table S1, available from the authors on request), will be used to predict targets and pathways of TSG and molecular docking will be used to explore the binding site and affinity between TSG and potential targets. Further pre-clinical research strategies based on this paper might be developed to encourage wider clinical applications of TSG or its derivatives safely and efficaciously.

Fig. 1: *Polygonum multijiorum* Thunb.

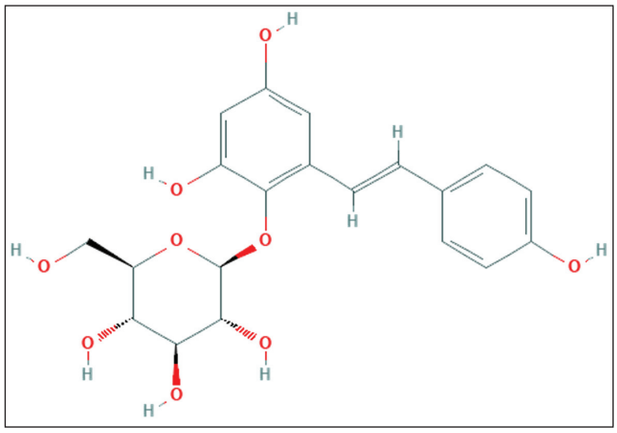

Fig. 2: Structure of TSG ($C_{20}H_{22}O_9$, PubChem CID: 5321884)

2. Pharmaceutics of TSG

Clinical applications of TCMs include raw and processed products. Different extraction or processing procedures of the same TCM may lead to different pharmacological effects. The most common processing for reducing toxicity and improve the potency of PMT is stewing or decoction with black bean sauce (Zhang and Yi 2014). Some studies suggested that TSG in PMT with a nine-time repeat steaming and sun-drying process was around 1%, contrasted with more than 3% of raw and 2% approximately with pharmacopeia method (Yang et al. 2015, 2018). In the processing of black bean sauce stewing, TSG content in PMT decreased regularly with the increase in processing times (Liu et al. 2013).

Traditional extraction processes include water extraction, diacolation, reflux extraction, ultrasonic extraction, microwave extraction and so on. Different extraction solvents had an effect on the contents of the critical compounds of PMT. TSG contents when extracted with water, 50% ethanol, 70% ethanol and 90% ethanol from 3 kinds of processed PMT were all higher than that of raw samples. TSG content was lowest when extracted with 90% ethanol (Zhu et al. 2018). TSG, undergoes visible light decomposition, is unstable at high temperature and under strongly alkaline conditions. Supercritical CO_2 extraction was used in recent years to extract TSG to avoid these problems (Zhang and Lan 2017). Principally, isolation and purification of TSG from the extracts of PMT are performed by the methods of chromatography, recrystallization, extraction and others. The purity of TSG reached 99% above with high-speed counter-current chromatography in laboratory (Yin et al. 2014).

3. Pharmacological effects of TSG

3.1. Effects on cardiovascular and cerebrovascular diseases

3.1.1. Atherosclerosis

TSG plays a role in the intervention and treatment of atherosclerosis by different mechanisms. Under TSG treatment, total cholesterol, total triglyceride, low density lipoprotein cholesterol and atherosclerosis index were significantly reduced, with effects similar to those of atorvastatin (Gao et al. 2007). As a chronic and progressive disease, atherosclerosis also results from vascular endothelial dysfunction, oxidative stress injury, chronic inflammatory infiltration and so on (Victor et al. 2009). TSG emerged vasodilative effects in mesenteric arterial rings via an endothelium-dependent pathway that involved inhibition of cyclooxygenase-2 (COX-2) and thromboxane A_2 (TXA_2) activities through opening a voltage-dependent K^+ channel, blockade of Ca^{2+} influx and release of intracellular Ca^{2+} (Jia et al. 2019). Endothelial dysfunction induced by oxidized low-density lipoprotein could be well treated with TSG via suppressing vimentin expression and cleavage and regulating the expressions of eNOS and iNOS, which might be concerned with the mechanism of atherosclerosis (Zhang et al. 2009; Yao et al. 2014). With the administration of oral gavage, TSG also suppressed expressions of matrix metalloproteinases (MMP) and inhibited inflammation in hyperlipidemic atherosclerotic rats (Zhang and Wang 2010). TSG showed an inhibitory effect on platelet derived growth factor-BB induced vascular smooth muscle cells proliferation, and the mechanism was concerned with the NO/cGMP/PKG pathway, which provided unequivocal evidence for the potency of TSG in atherosclerosis (Xu et al. 2012).

With chemical fingerprints and anti-platelet aggregation bioactivity test for spectrum-effect correlation analysis, TSG was considered to be the main active substance of PMT in inhibiting platelet aggregation *in vitro* (He et al. 2017). Potential mechanisms involve the inhibition of platelet FcγRIIa, AKT and GSK3β phosphorylation and platelet Ca^{2+} (Xiang et al. 2014).

3.1.2. Myocardial injury

TSG has potent cardioprotective effects. TSG induced proliferation of cardiac stem cells *in vivo* and *in vitro via* increasing the expressions of stem cell antigen-1, cardiac troponin-I, GATA-4, Nkx2.5, and connexin 43 protein, which indicated a potential treatment strategy of TSG for stimulating endogenous stem cells to help to repair heart function after myocardial infarction in patients (Song et al. 2015 and 2016). TSG reduced p-MEK and extracellular signal-regulated kinase (ERK) 1/2, decreased overall production of extracellular matrix components and ROS generation and consequently suppressed angiotensin (Ang) II-induced cell proliferation. Thus, TSG might be useful in the prevention of cardiac fibrosis (Zhang and Chen 2012). Similarly, cardiac fibrosis in pressure-overloaded rats was improved by TSG with the potential mechanism of upregulation of endogenous peroxisome proliferator-activated receptor-γ (PPAR-γ) expression (Peng et al. 2016). Cardiac remodeling induced by pressure overload in rats could also be inhibited through the suppression of transforming growth factor-β1 expression and ERK 1/2 and p38 mitogen-activated protein kinase (MAPK) activation (Xu et al. 2013). TSG could improve myocardial ischemia/reperfusion injury *in vivo* and *in vitro via* activating the Notch1/Hes1 signaling pathway and attenuating endoplasmic reticulum stress-induced apoptosis (Zhang and Yu 2017). In the new research, cell apoptosis in H9c2 *in vitro* was suppressed by TSG in connection with the Bcl-2/Bax ratio, caspase-3, and AKT activation (Sun et al. 2019).

3.1.3. Cerebral ischemia/ reperfusion injury

In animal models with cerebral ischemia/reperfusion (I/R) injury, TSG was implemented to protect cerebral neuron and inhibit neural apoptosis. TSG showed potent calcium antagonistic effects and inhibited the overload of calcium in cells for cerebral neuron protection (Grech et al. 1994). Apoptosis is the most important pathophysiological effect in cerebral I/R injury. TSG could cross the blood-brain barrier and affect many factors to suppress apoptosis and then protect cerebral tissue. Cerebral I/R injury in mice was well protected with TSG *via* inhibiting NOX4 expression, thereby decreasing ROS levels and resisting over-expression of cleaved caspase-3/9 (Xue et al. 2019). The protection might be also related to the expressions of apoptosis-related factors like p53, Bcl-2, Bax regulated by TSG (Wang et al. 2018). It was demonstrated that 5-hydroxytryptamine (5-HT) was one of biomarkers of chronic cerebral injury *via* the change of level and functions. Release of 5-HT and expression of uncoupling protein 4 were increased, activity of 5-HT transporter was enhanced and 5-HT receptor 2A was inhibited, which might be the mechanism of TSG in the treatment of cerebral I/R injury in rats (Yi et al. 2019). TSG upregulated the expressions of vascular endothelial growth factor, Ang 1 and Ang receptor 2 to accelerate angiogenesis and recovery process of cerebral infarcts (Mu et al. 2017).

3.2. Effects on the nervous system

3.2.1. Alzheimer's disease

Alzheimer's disease (AD), a neurodegenerative condition, is characterized by a progressive decline in cognitive ability. Clin-

ical manifestations are similar to dementia in TCM. TSG exerted apparent neuroprotective effects. TSG might reduce cognitive deficits in AD animal models as shown in a systematic review (Sheng et al. 2016). With the treatment of TSG, the passive avoidance test of rats and the increased escape latency time of mice were all displayed a striking decrease (Luo et al. 2009; Xie et al. 2018). TSG could modulate amyloid precursor protein (APP) processing *via* activation of AKT-GSK3β pathway in cells and in APP/PS1 transgenic mice (Yin et al. 2018). Over-expression of APP induced by aluminum exposure and β-amyloid production were also suppressed with administration of TSG (Luo et al. 2009; Zhang and Zhang 2018). Mitochondrial functions and neurotrophic factors releasing were enhanced to block or slow AD progression. TSG ameliorated hippocampal neuronal cell injury by restoring mitochondrial function *via* Nrf2-HO-1 pathway. TSG also improved the learning, memory and behavior abilities *via* increasing the expression of NR2B receptors and Fyn (Luo et al. 2016).

3.2.2. Parkinson's disease

Parkinson's disease (PD), one of the most common neurodegenerative diseases, is similar to tremor syndrome in TCM. Factors (like oxidative stress, neuroinflammation, mitochondrial dysfunction, apoptosis, dysregulated kinase signaling, etc.) were considered to be reasons leading to PD (Sun et al. 2011). ROS increasing and JNK phosphorylation were blocked when 1-methyl-4-phenylpyridinium (MPP^+)-induced apoptosis in PC12 cells was treated with TSG. That means that the inhibition of ROS generation and modulation of JNK activation may be the underlying mechanism of mediating the anti-apoptotic effects (Li and Li 2010). Dopamine (DA) neuronal injury in rats, elicited with 6-hydroxydopamine (6-OHDA), was protected by TSG through inhibiting microglia-elicited neuroinflammation (Huang et al. 2018). Regulating ROS-NO and PI3K/AKT signaling pathways might be other ways for TSG to protect PC12 cells from 6-OHDA-induced apoptosis (Tao et al. 2011; Qin et al. 2011). In recent reports, DA neurons were protected by TSG against lipopolysaccharide-induced neurotoxicity via dual modulation on glial cells by attenuating microglia-mediated neuroinflammation and enhancing astroglia-derived neurotrophic effects (Zhou et al. 2018). Taken together, TSG may be a potential drug for PD.

3.2.3. Depression

Depression is a common mental disorder with typical symptoms comprising black mood, thinking retardation, interest loss, anorexia, sleeping disorder, cognitive impairment and other physical symptoms (Kupfer et al. 2012). Animal models are usually established with stress, drugs, surgery, and genetic modification (Wang and Timberlake 2017). Forced swim test (FST) and tail suspension test (TST) are reliable methods for antidepressants screening in the experiments of behavioral pharmacology. TSG exerted antidepressant effects expressed as reduced immobility time. Ptosis and body temperature reduced by reserpine were reversed and locomotor activity was enhanced (Wu et al. 2013; Zhou and Zhang 2015). In FST, TST and open-field test, oxidative stress-related markers (MDA, GSH, GSH-PX, and total antioxidant capacity), nitrosative stress-related markers (NOS-2, nitrite content) and inflammatory markers (TNF-α, IL-1β, IL-6, and NOS-2) were assayed. At the same time, the expressions of brain-derived neurotrophic factor (BDNF), doublecortin, glial fibrillary acidic protein and P-AKT were all detected to be upregulated. In a word, these results demonstrated antidepressant effects of TSG through oxido-nitrosative stress and inflammatory pathways (Chen et al. 2017; Jiang et al. 2018).

3.3. Anti-aging properties

TSG had a good effect on prolonging the life span of Drosophila, natural and pathological aging mice. This was associated with regulating the functions of klotho and the neural insulin/ insulin-like growth factor-1 (IGF-1) signaling pathway (Zhou and Yang 2015). Meanwhile, sirtuin 1-mediated longevity pathway was modulated by TSG to enhance health conditions in aging mice (Ning et al. 2018). TSG also improved vascular senescence *via* increasing the activity of sirtuin 1 *in vivo* and *in vitro* (Jiang et al. 2018). TSG has been exerted the effect of anti-skin-aging through increasing collagen fiber and suppressing insulin/ IGF-1 signaling pathway (Han et al. 2012). TSG exerted great hair regrowth effect in alopecia and promoted melanin biosynthesis, which means TSG may be an alternative medicine for the treatment of hair loss (Jiang et al. 2009; Zhou et al. 2014).

3.4. Other diseases

3.4.1. Diabetes and its complications

Streptozotocin-induced diabetic nephropathy (DN) in rats could be ameliorated by intraperitoneal injection of TSG via alleviating oxidative stress injury, anti-inflammatory action, anti-aging effects, etc. (Li and Cai 2010; Nian et al. 2015; Mei et al. 2017; Pang et al. 2019). Otherwise, TSG could inhibit cell apoptosis and oxidative stress *via* downregulating IL-1β expression for protecting podocytes, which is activated by NLRP3 inflammasome (Li and Wang 2018). Gastrointestinal dysfunction could be relieved by treatment with TSG in diabetic mice *via* upregulating SIRT1 and PPAR-γ expressions, which suggested TSG to be a promising therapeutic agent for treating diabetic gastrointestinal dysmotility (Chang et al. 2012). TSG could alleviate lipids accumulation and oxidative stress in skeletal muscle of high fat diet and streptozotocin-induced type 2 diabetes rats, and then improve insulin resistance and glucose and lipid metabolism disorder (Wang and Fan 2016).

3.4.2. Osteoporosis

Under oral administration of TSG, bone mineral content and bone mineral size in the bone tissues of normal rats were well increased and the resistance to exogenic action, structural toughness and strength were significantly enhanced, which means that TSG had the potential of preventing and improving osteoporosis (Hu et al. 2011). Bone loss and bone destruction were significantly reduced under the administration of TSG to ovariectomized mice (Kim et al. 2018). In mechanism studies, the protection of TSG for osteoblastic MC3T3-E1 cells induced by hydrogen peroxide was associated with oxidative stress, while the immune system, the chemokine signaling pathway and cell proliferation and differentiation may be also involved (Zhang 2012, 2018; Fan et al. 2018).

3.4.3. Tumor

Natural flavonoids have been shown to exert anti-tumor effects for many years. TSG, as one of them, has a significant inhibitory effect on tumor angiogenesis (You and Zhang 2018). Now ulcerative colitis (UC) is accepted to be a precancerous lesions of colorectal carcinoma (CRC) and the risks of UC patients accompanied with CRC are concerned with their course (Westbrook et al. 2010). Oxidation and inflammation are concerned with the progress of CRC. TSG could suppress the abilities of proliferation, metastasis, motility, migration and promote apoptosis of HCT116 and SW480 cells via depressing the PI3K/AKT/NF-κB signaling pathway (Lin et al. 2016; Li et al. 2017, 2018). Furthermore, TSG exerted a synergistic effect with ADM on anti-breast cancer through the inhibition of VEGF/PI3K/AKT pathway (Shen et al. 2018).

4. Prediction of targets and pathways

4.1. Targets analysis

According to the 3D structure of TSG explored from PubChem (https://pubchem.ncbi.nlm.nih.gov/), in total 189 human proteins (Table S2, available from the authors on request) were collected as candidate TSG targets from PharmMapper server with Zscore ≥0 (Wang and Shen 2017). Protein-protein interaction (PPI) network was constructed by STRING database with a combined score > 0.700 and "Homo sapiens" and visualized

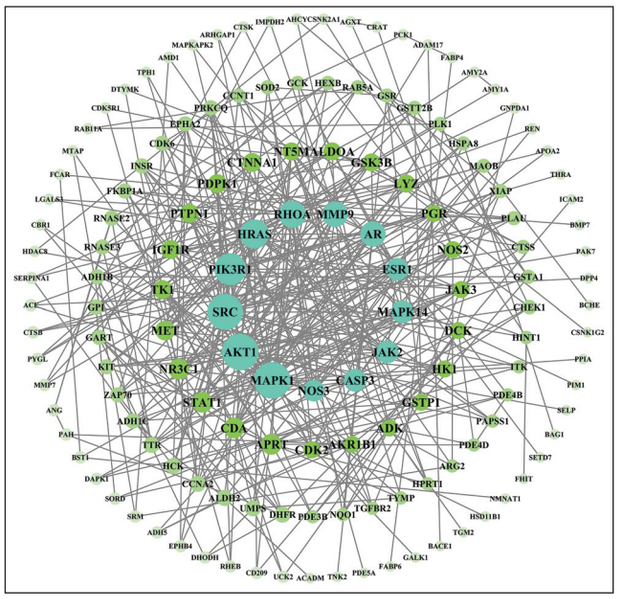

Fig. 3: PPI network of TSG. 146 green circles represented the targets and 417 edges represented interactions between targets.

by Cytoscape software (Fig. 3). Regardless of discrete targets, there were 146 targets in the PPI network. Eight core targets, including AKT1, AR, HRAS, MAPK1, MMP9, PIK3R1, RHOA, and SRC, were obtained with CytoHubba analysis (Fig. 4A). The results of MCODE obtained the top two most significant modules with score of 5.778 and 5.048 (Fig. 4B). Convincingly, two modules comprised eight core genes obtained from CytoHubba analysis, which further confirmed that the importance of these targets (Chin et al. 2014).

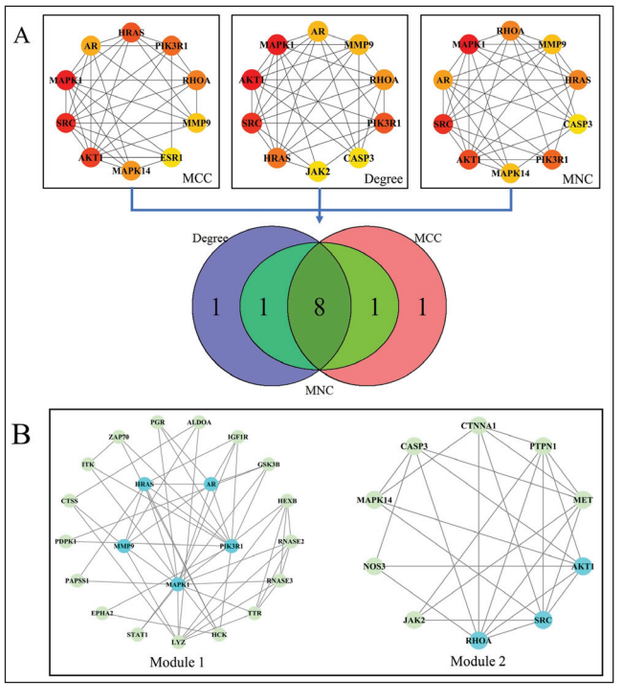

Fig. 4: Core targets were explored by CytoHubba and MCODE plugins. (A). PPI network was analyzed by CytoHubba ranked by MCC, degree, and MNC, and overlapping targets were got to represent core targets by a Venn diagram. (B). Two most remarkable modules were analyzed by MCODE, and the circular nodes colored cyan represented core targets.

4.2. *Pathways analysis*

All targets in the PPI network were subjected to KEGG pathway analysis using Metascape database. The results revealed a total of 127 enriched pathways (*P,* 0.01, Table S3, available from the authors on request), related to cancer, metabolism, cell functions, immune, neuro-regulation, exogenous infection, endocrine system and other signaling pathways. The most significantly enriched pathways were tose related to in cancer, PI3K-Akt signaling pathway, FoxO signaling pathway, insulin signaling pathway, proteoglycans in cancer, etc. (Fig. 5).

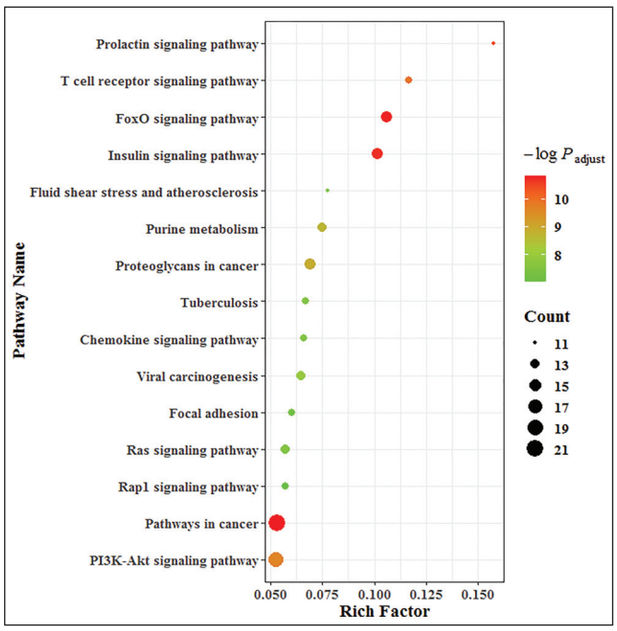

Fig. 5: KEGG pathways of TSG. The enrichment was visualized by R 4.0.2 software: the gradual color of spots represented the negative logarithm of *P* adjusted value and the size represents the target number enriched in the pathways.

4.3. *Molecular docking and analysis of binding sites*

With the performance of molecular docking by Autodock Vina, the affinities of TSG with AKT1, MMP9, MAPK1, HRAS, SRC, RHOA, AR, and PIK3R1 were calculated and showed in Table 1. Most of affinities between TSG and proteins were similar to those between proteins and their original ligands. The main amino acid residues in AKT1, MMP9, MAPK1 that interacted with TSG were explored with a Python script. As shown in Fig. 6, hydrogen bonds, hydrophobic interactions, π-cation interactions and π-π stacking were the main forms of interactions between TSG and core targets.

5. Toxicity of TSG

PMT, one of the most common traditional Chinese medicines, is also well known for its hepatotoxicity (Wu et al. 2012). With the method of pharmacogenomics, the HLA-B*35:01 allele was first considered to be the specific biomarker for PMT-induced liver injury, which elucidated the molecular mechanisms (Li et al. 2019). Currently, the toxicity of TSG has been investigated and the results are summarized in Table 2.

TSG was one of the hepatotoxic ingredients because the change trend of TSG content was similar to hepatotoxic potential (Yu et al. 2017). Liver injuries caused by PMT cannot be attributed to a single component, but to many polyhydrostilbenes, anthraquinones and tannins jointly (Xu et al. 2017). TSG content was positively correlated with idiosyncratic liver injury and it was demonstrated to be the major factor for PMT-induced liver injury by inducing immunological idiosyncratic hepatotoxicity via the suppression of PPAR-γ in a rat model of idiosyncratic drug-induced liver injury

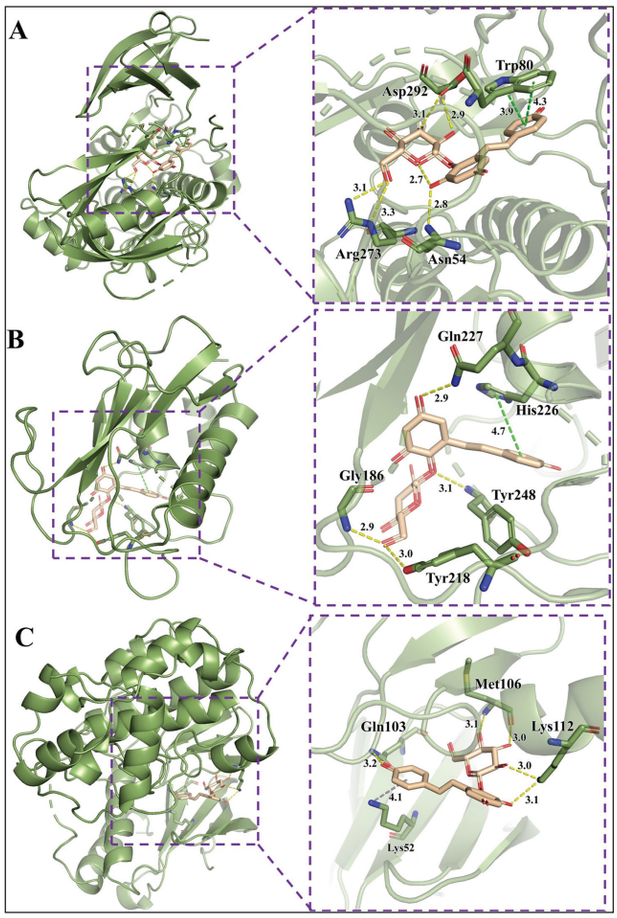

Fig. 6: Molecular docking analysis of TSG binding to core targets. (A) TSG act on AKT1, (B) TSG act on MMP9, (C) TSG act on MAPK1. The dashed lines colored yellow, green and gray represented hydrogen bonds, π-π stackings, and π-cation interactions respectively, with interaction distances indicated above the lines. In the three-dimensional structural analysis, TSG is presented as colored stick models, while the residues interacting with proteins are marked with green.

found that TSG was a greater contributor than other components and might be the most important one (Meng et al. 2017). Previous results demonstrated that TSG could suppress the phase II metabolism of emodin *in vivo via* the pathway of downregulating UGT1A8 mRNA expression (Zhang and Bai 2017). In the research of pharmacokinetics, the accumulation of emodin *in vivo* with repeated administration of 20 g/kg PMT extract was ascribed to the interaction of metabolism between TSG and emodin (Zhang et al. 2013). TSG could promote the absorption of emodin and inhibit the glucuronidation of emodin in Caco-2 cells *via* the influence of sodium-dependent glucose cotransporter 1 and exported *via* multidrug-resistant protein 2 and inhibit the metabolism of emodin in human hepatoma HepG2 according to the content change of emotion detected by liquid chromatography coupled with mass spectrometry. Taken together, the assumption about PMT-induced liver lesions based on the above results could be put forward: TSG might enhance absorption from the intestines and inhibit the liver metabolism of emodin, thereby causing cellular accumulation (Wang et al. 2019). In addition, although TSG alone had no obvious hepatotoxicity, TSG enhanced expressions of hepatic CYP3A4, CYP2E1 and CYP1A2 and aggravated acetaminophen-induced hepatotoxicity in mice (Ma and Zheng 2015).

Ranitidine have been proven to induce idiosyncratic hepatotoxicity in animal models induced by lipopolysaccharide (LPS). Similarly, cis-TSG with LPS not only increased ALT and AST levels in rat plasma and liver tissues contrasted with LPS group, but also enhanced the expressions of TNF-α, IL-1β, IL-6 and interferon-γ and inhibited PPAR-γ expressions, whereas trans-TSG did not show analogical effects. According to the above results, TSG could potentiate liver lesions with a non-hepatotoxic dose of LPS in rats though downregulating PPAR-γ. Meanwhile, pioglitazone could suppress cis-TSG/LPS-induced hepatotoxicity, which meant that pioglitazone could use to prevent hepatic side effects induced by cis-TSG containing herbs in clinical practice (Ma et al. 2013).

In summary, although TSG has little toxicity, drug-drug interactions are the main path to produce liver injury, which is a revelation to us that we should also take an eye on the interactions while observing the pharmacology and toxicology of the drug itself.

Table 1: Affinities of TSG with core targets

Targets	PDB ID	PubChem CID of original ligands	Affinity with TSG (kcal/mol)	Affinity with original ligand (kcal/mol)	Standard (kcal/mol)
AKT1	5KCV	53262401	-10.0	-11.0	
MMP9	6ESM	133084111	-9.7	-10.7	
MAPK1	2OJG	1473242	-9.3	-8.8	Good: ≤ -1.2
HRAS	1P2U	135403657	-8.7	-9.8	Better: ≤ -5.0
SRC	4MXO	5328940	-8.4	-8.5	Best: ≤ -7.0
RHOA	5C4M	135398619	-8.1	-7.8	
AR	3B65	24892823	-7.5	-8.4	
PIK3R1	1PBW	—	-6.8	—	

(Ma et al. 2013; Lin et al. 2019). In the exploration of bilirubin metabolism mediated by glucuronidation of UDP-glucuronosyltransferases 1A1 (UGT1A1), TSG inhibited UGT1A1, but the inhibitory effect of phase II metabolic enzyme UGT1A1 disappeared after phase I metabolism (Hu et al. 2011).

The relationship of spectrum-toxicity was analyzed via rough set theory and idiosyncratic hepatotoxicity *in vitro* and it was

6. Discussion and further perspectives

As a common TCM, PMT has a long medicinal history with high pharmaceutical values and gains the reputation of rejuvenating oneself and prolonging life. Raw PMT has the functions of detoxification, preventing attack of malaria, bowel-lubricating and defecation-promoting while processed PMT plays a role in replenishing

Table 2: Progress of TSG-induced hepatotoxicity

Animal/cell	Model/stimulation	Time	Indexes	References
SD rats	TSG, 150, 300 and 600 mg/kg, ig	90 days	AST, ALT, GLB ↑, ALB, A/G ↓, liver histology	(Hu et al. 2011)
Male KM mice	TSG, 10 and 40 mg/kg, ig	3, 5, 7 days	CYP2E1 ↑, CYP1A2, CYP3A4, CYP4A14 ↓	(Zhang et al. 2013)
L-02 cells	TSG, 30~1500 mg/L	4 hours	Cell inhibition rate and apoptosis rate ↑	(Lin et al. 2019)
Male Wistar rats	TSG (117 mg/kg, ig, 1 week) + emodin (82.4 mg/kg, ig)	—	AUC, Cmax and T1/2 of emodin, UGT1A8, UGT1A2 ↑, UGT1A1, UGT1A6, UGT1A9 ↓	(Ma et al. 2013)
Caco-2 cells	TSG (10 and 100 μmol/L) + Emodin (10 μmol/L)	24 hours	Concentration, UGT1A8, UGT 1A10, and UGT 2B7 ↓	(Yu et al. 2017)
Male SD rats	Cis-TSG (0.35% and 0.70%, ig) + LPS (2.8 mg/kg, iv)	Once	AST, ALT, TNF-α, IL-6, apoptosis rate ↑, PPAR-γ ↓, liver histology	(Zhang and Bai 2017)
SD rats	Cis-TSG (50 mg/kg, ig) + LPS (2.8 mg/kg, iv)	Once	AST, ALT, TNF-α, IL-1β, IL-6, IFN-γ, apoptosis rate ↑, PPAR-γ ↓, liver histology	(Meng et al. 2017)
Male C57BL/6 mice	TSG (200, 400, 800 mg/kg, ig) + Acetaminophen (200 mg/kg, ig)	Once	AST, ALT, CYP1A2, CYP2E1, CYP3A4 ↑, liver histology	(Xu et al. 2017)
L-02 cells	TSG (100 μmol/L) + Acetaminophen (0.48, 1.2, 3.0 mmol/L)	24 hours	CYP1A2, CYP2E1, CYP3A4, AHR and PXR ↑	(Xu et al. 2017)

vital essence and blood, reinforcement of kidney and blackening the beard and hair. Modern research has indicated that PMT has remarkable pharmacological activities on the aspects of anti-cardiovascular disease, lipid-lowering, anti-inflammation, anti-oxidative stress, anti-aging, immunity enhancement, etc. (Wu and Sun 2017). On this basis, PMT and related products are promising to be developed into drugs for hypertension, hyperglycemia, ischemic cerebral injury, atherosclerosis. Unfortunately, many Chinese patent medicines containing PMT were associated with adverse drug reactions, including gastrointestinal reaction, dry mouth, liver damage, allergic reactions, and palpitations (Yang et al. 2017).

TSG content is higher than that of other chemical components in PMT. However, TSG exists in two forms: cis-TSG and trans-TSG and more than 90% are trans-structure. TSG is light sensitive and the trans-structure can convert into cis-structure in lighting conditions.

As a biologically active natural component extracted from PMT, TSG plays an essential role in the chemical components of PMT, because it contains multiple pharmacological activities, including cardiovascular protection, neuroprotective properties, anti-senility effect, anti-diabetes, anti-inflammatory and so on. A variety of diseases were significantly treated with TSG, such as atherosclerosis, AD, PD, cerebral I/R injury, diabetes, osteoporosis, colitis, periodontitis. Recently, numerous milestones have been made in the pharmacologic mechanism of TSG. The results of network pharmacology and molecular docking also show a lot of bioactivities of TSG via many targets and pathways.

TSG has shown prospective pharmacological activities, particularly as an agent of cardiovascular protection and neuroprotection, which exerts that TSG has a higher applied value and development prospects for senile diseases. Currently, more attention should be devoted to exploring how to explore and prevent underlying toxicity of TSG and establish an early warning system. What's more, we should make every effort in translating the effects into clinical applications appropriately.

7. Conclusions

The present review makes a summary of research progress of TSG, mainly including the promising pharmacological effects and underlying toxicity. TSG has a wide range of pharmacological effects and is a promising therapy for diseases of the cardiovascular and nervous system. Although pharmacological mechanisms of TSG have been widely investigated, toxic effects of TSG are also reported. Therefore, more explorations of potential toxicity and mechanisms will be urgently needed in the future, especially regarding liver injury induced by drug-drug interactions. After the review, we hope that further investigations about pharmacological and toxic mechanisms of TSG will illuminate the influence and mechanisms of TSG, which provides us thoughts for translating the effects of TSG into clinical applications appropriately.

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Data availability: The relevant databases, software, drug targets and KEGG pathway names are available in the Supplementary Source files available from the authors or the publisher.

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