Review of clinical studies of *Polygonum multiflorum* Thunb. and its isolated bioactive compounds

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ABSTRACT

Polygonum multiflorum Thunb. (PMT), officially listed in the Chinese Pharmacopoeia, is one of the most popular perennial Chinese traditional medicines known as He shou wu in China and East Asia, and as Fo-ti in North America. Mounting pharmacological studies have stressed out its key benefice for the treatment of various diseases and medical conditions such as liver injury, cancer, diabetes, alopecia, atherosclerosis, and neurodegenerative diseases as well. International databases such as PubMed/Medline, Science citation Index and Google Scholar were searched for clinical studies recently published on *P. multiflorum.* Various clinical studies published articles were retrieved, providing information relevant to pharmacokinetics-pharmacodynamics analysis, sleep disorders, dyslipidemia treatment, and neurodegenerative diseases. This review is an effort to update the clinical picture of investigations ever carried on PMT and/or its isolated bio-compounds and to enlighten its therapeutic assessment.

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INTRODUCTION

Plants, herbs, and ethnobotanicals have been selected and used empirically as drugs for centuries, initially as traditional preparations then as pure active principles, with the knowledge and accumulated practice passing from generation to generation.[1,2] Medicinal plants are plants containing the substance that are used for therapeutic purposes or which are precursors for the synthesis of useful drugs.[3] Herbal Medicinal can be categorized into two broad parts. The first one includes complex of mixture containing a wide variety of compounds (e.g.: Infusions, essential oils, tinctures or extracts), and the second category refers them as pure, chemically define active principles.[4]

Polygonum multiflorum Thunb. (PMT, Polygonaceae family, Figure 1), well known as He shou wu in China and Fo-ti in North America,[5] is one of the most popular perennial Chinese traditional medicinal vine-like herbs, officially listed in the Chinese Pharmacopoeia.[6] Various parts of the plants were utilized for different medicinal purposes. The leaves [Figure 2a], root tuber [Figure 2b] and rhizomes [Figure 2c] of this plant have been used as tonic and anti-aging agents[7-12] whereas the stem [Figure 2d] is used to alleviate insomnia and even to have an antidiabetic therapeutic activity as well.[13-15]

Laboratory studies and clinical practice have demonstrated that PMT possesses various biological and therapeutic actions, including anti-tumor,[16,17] antibacterial,[18] anti-inflammatory,[13] anti-oxidant,[19-21] anti-HIV,[22] liver protection,[23,24] nephroprotection,[25] antidiabetic,[15,26] anti-alopecia,[27,28] and anti-atherosclerotic activities.[29,30] It has been also reported to exert preventive activity against neurodegenerative diseases,[31-35] cardiovascular diseases and to reduce hyperlipidemia as well.[36,37]

The clinical efficacy, as well as the safety of PMT and its bioactive products, has attracted much attention in the recent years; due to the increasing reports of various cases on hepatotoxicity,[38-42] published worldwide. In the present review, the advancements in thorough investigation of clinical studies and pharmacokinetics (PKs)-pharmacodynamics (PDs) profile of *P. multiflorum* are discussed, meanwhile describing the

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clinical features of this particular herbal-induced liver injury. This report will enlighten the broad understanding on the clinical therapeutic evaluation of PMT or other herbal drug containing quite the same phytochemical components.

METHODOLOGY

An electronic search was performed by searching several databases: PubMed (Medline), Highwire, HerbMed, Google Scholar, Scopus, Cochrane Database of Systematic Reviews and Cochrane Library using key terms including, "PMT," "He shou wu," "Shou-Wu-Pian," "Shen-Min," "Fo-Ti," and "clinical study," "humans," "patients," "case report," "hepatotoxicity" to identify English-language publications (case reports, case series, prospective study and clinical review articles) and abstracts published regarding *P. multiflorum* and/or its compounds. Furthermore, we scanned the references lists of the primary articles to identify the publications not retrieved by electronic research. A total of 54 publications were identified, and the results compiled. They showed 7 articles relevant to clinical PKs-PDs analysis, 2 to anti-inflammatory effect, 2 for dyslipidemia treatment, 2 relevant to sleep disorders, 3 for neurodegenerative diseases and 52 patients with hepatotoxicity due to *P. multiflorum* ingestion. The quality of clinical studies on *P. multiflorum*, the characteristics and outcomes of patients reported with herbal hepatotoxicity and the *P. multiflorum* claimed pharmaco-therapeutic values are reviewed and discussed in this paper.

CLINICAL PHARMACOKINETICS AND PHARMACODYNAMICS STUDIES OF *POLYGONUM MULTIFLORUM* EXTRACTS AND/OR ITS BIOACTIVE COMPONENTS

Herbal medicines are mixtures of more than one active ingredient. The multitude of pharmacologically active compounds obviously increases the likelihood of interactions taking place. Hence, the likelihood of herb-drug interactions is theoretically higher than that of drug-drug interactions, if only because synthetic drugs usually contain single chemical entities.[43] Case reports and clinical studies have highlighted the existence of a number of clinically important interactions, although cause-and-effect relationships have not always been established. Herbs and drugs may interact either pharmacokinetically or pharmacodynamically [Figure 3].[44]

To date, a number of *in vitro* studies have addressed the potential of selected herbal extracts and/or specific constituents to inhibit or induce drug-metabolizing enzymes or transporters, especially cytochrome P450 (CYP450) isoforms and P-glycoprotein (P-pg). However, translation of *in vitro* data in a clinical setting is hard to accomplish, and discrepancies are often observed between predicted outcomes on the basis of the *in vitro* studies and results of controlled clinical studies.[45]

Several pharmacological and clinical studies have been done to investigate the PK-PD parameters analyzes of PMT and/or its bioactive components. In 2002, some Korean scientists conducted a clinical PK study about rhein; one of the main bioactive of PMT.[46] This research produced some interesting findings, enlightening that in terms of the bioavailability, while the levels in aloe-emodin, emodin, and chrysophanol [Figure 4] in herbal extracts were much higher than rhein level, only rhein was selectively absorbed by the body even if rhein is structurally similar to other anthraquinones.[46] These findings corroborate the results of another clinical study published a decade earlier by Krumbiegel and Hu.[47] This phenomenon can be explained by one of the three following possibilities. The first one is that rhein are formed when sennosides

Figure 1: *Polygonum multiflorum* Thunb

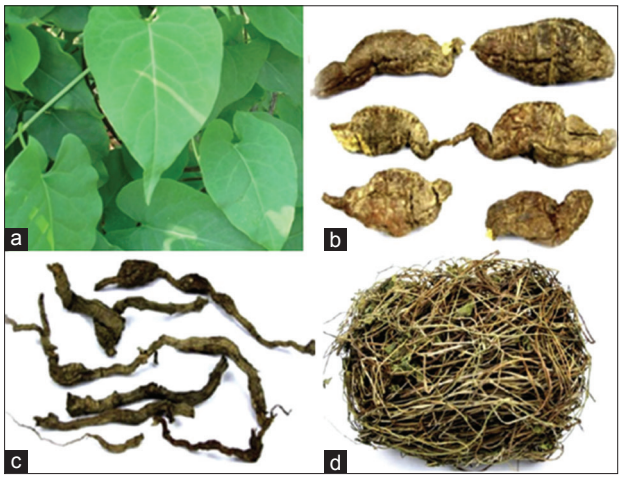
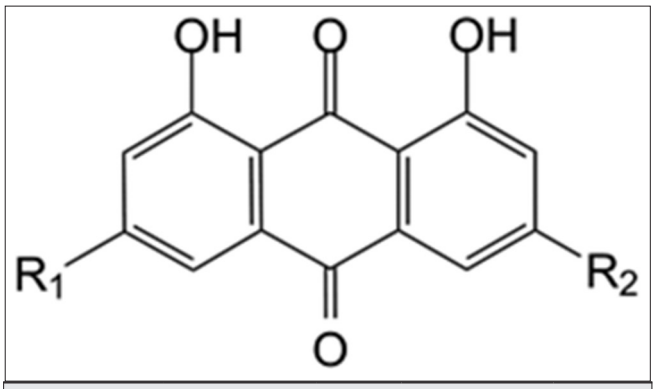


Figure 2: Photos of (a) leaves, (b) tuber roots, (c) underground rhizomes and (d) stem from *Polygonum multiflorum* Thunb

(e.g.: Sennoside A, Figure 5) are decomposed by bacteria in the intestines,[48] but the time courses of plasma rhein concentrations render this possibility highly improbable. The second possibility is that sennosides are metabolized by intestinal bacteria into anthrones [Figure 6], and the sulfoconjugation or glucoronidation occurs leading to the excretion of the substance through urine.[46] The third possibility stressed out the fact that rhein can be easily bio-transformed from aloe-emodin.[47,49] Furthermore, in another clinical investigation, the high bioavailability of rhein was assessed using the routes of administration as comparative key of the research. The findings suggested that after a single dose of herbal extract, the oral bioavailability of rhein was significantly higher than its rectal bioavailability.[50] By analysis of the route administration, the absorption of weak acids such as rhein may be optimal in the acidic environment of the stomach, whereas their absorption might be unfavorable in the relatively alkaline situation of the small intestine. Retention enema therapy requires multiple, higher daily doses due to poor bioavailability if the same plasma rhein concentration as oral therapy is to be achieved.[50]

Herbal medicines constituents may affect the function of the drug-metabolizing enzymes by inhibiting through different, yet not completely disclosed mechanisms, the catalytic activity of specific enzymes, or they may simply compete for binding. In either case, increase in oral bioavailability and/or reduction of hepatic clearance of the affected drugs are expected to occur, thus leading to an increase in the plasma drug levels, which may expose the patient to a serious risk of adverse drug toxicity.[45] The drug transporters and drug-metabolizing enzymes involved in the *in vivo* process, the modulatory effects on both P-pg [51-53] and CYP450 isoenzymes[54,55] and the acute toxicity[39,56-60] of PMT and/or its major bioactive compounds are all well documented. P-gp-based drug interactions are a major concern in the clinic and in preclinical drug development, especially with respect to the intestinal absorption of drugs and distribution of drugs across the liver, kidney, intestine and blood-brain barrier.[61] Despite the widespread use of herbal medicines, documented herb-drug interactions are spare. However, studies on common herbs indicate that significant herb-drug interactions exists.[62] Several commonly used traditional Chinese medicine (TCM) have been reported to interact with P-gp. For example, St. John's wort was found to increase the duodenal P-gp expression by 1.4-fold in healthy volunteers after multiple oral administrations. It



Compound	R1	R2
Aloe-emodin	H	CH_2OH
Chrysophanol	H	CH_3
Danthron	H	H
Emodin	OH	CH_3
Physcion	OCH_3	CH_3
Rhein	H	COOH

Figure 4: Chemical structures of aloe-emodin, chrysophanol, danthron, emodin, physcion and rhein

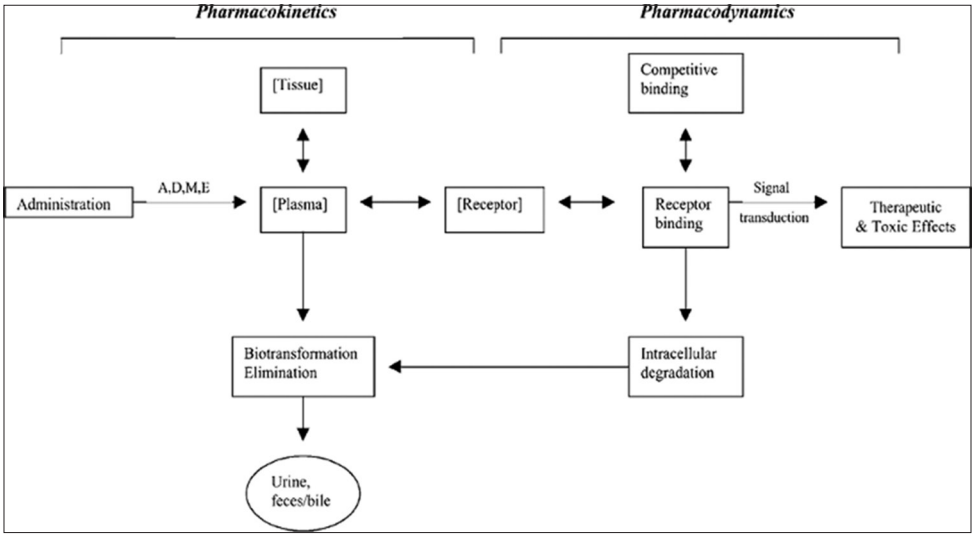


Figure 3: Schematic representation of the physiologic processes determining drug disposition in the human body and the relationship of pharmacokinetics and pharmacodynamics to these processes (A: Administration, D: Distribution, M: Metabolism, E: Excretion)

was also reported that St. John's wort could result in an 18% decrease of digoxin exposure after a single oral dose of digoxin (0.5 mg).[53,63] Li *et al*. investigated the inhibitory effect of PMT constituents on P-pg mediated the digoxin transport in MDR1-MDCKII cells. The herbal constituents tested were trans-Resveratrol [Figure 7], 2,3,5,4'-tetra hydroxylstilbene-2-O-β-D-glucoside (TSG, Figure 8), emodin, chrysophanol, aloe-emodin, and physcion. Among the various constituents of *P. multiflorum* tested, emodin was significantly the strongest inhibitor of P-gp (IC_{50} = 9.42 μM) in MDR1-MDCKII and Caco-2 cells.[53] Furthermore, clinical study findings enlightened emodin to be found to possess the strongest promising effect for overcoming P-gp mediated steroid resistance by inhibiting the P-gp efflux function.[51]

Genetic polymorphisms in the CYP450 enzyme also contribute to differences in an individual's ability to metabolize herbal medicines. The use of concurrent medications that either inhibit or induce one or more isoforms, which may result in significant changes in the rate of drug clearance, is one of the major reason for altered CYP450 activity.[44,64] CYP450 1A2 (CYP1A2) and CYP450 3A4 (CYP3A4) are involved in the metabolism of xenobiotic in the body,[65,66] their expression appear to be induced by various herbal medicines and/or dietary constituents.[67] The genotype and the allelic frequencies of CYP1A2 were evaluated in Chinese patients with acute liver injury induced by *P. multiflorum* in order to investigate CYP1A2 allele polymorphism association with the hepatotoxicity from PMT.[55] The findings revealed that the frequency of the CYP1A2 * 1C mutation in Chinese patients with *P. multiflorum*-induced acute liver injury differed significantly from that in healthy Chinese people, indicating that CYP1A2 * 1C is probably related to metabolism of PMT, which is, followed by acute liver injury.[55] Moreover, despite the structural similarity and/or identical molecular weight of various herbal constituents, emodin significant inhibited CYP3A4/5 activity.[53] Considering *P. multiflorum* and/or its constituents as relative toxic compound, potential drug-herb/herb-herb interactions based on CYP and P-gp should be taken into account when using this herbal medicine in the clinic. By fully appreciating the nature of PKs, PDs principles, and drug-herb interactions, healthcare professionals can drastically reduce unwanted side effects and at the same time enhance the therapeutic efficacy and usefulness of herbal medicines.

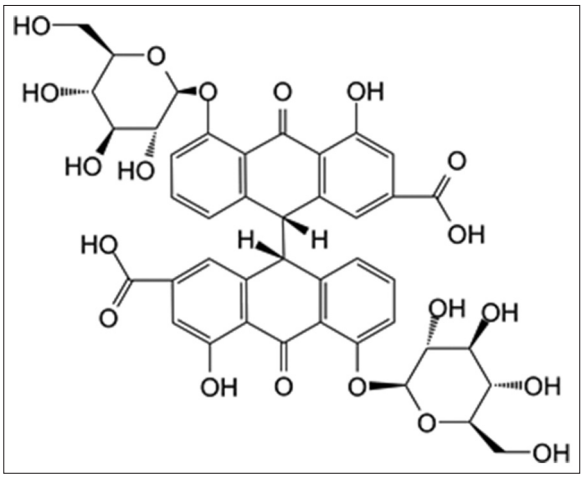


Figure 5: Chemical structure of sennoside A

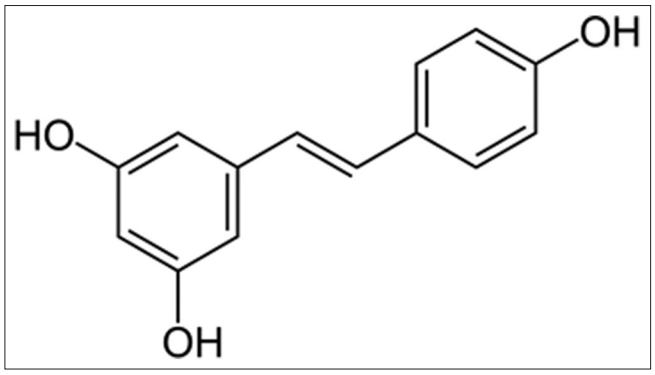


Figure 7: Chemical structure of trans-resveratrol

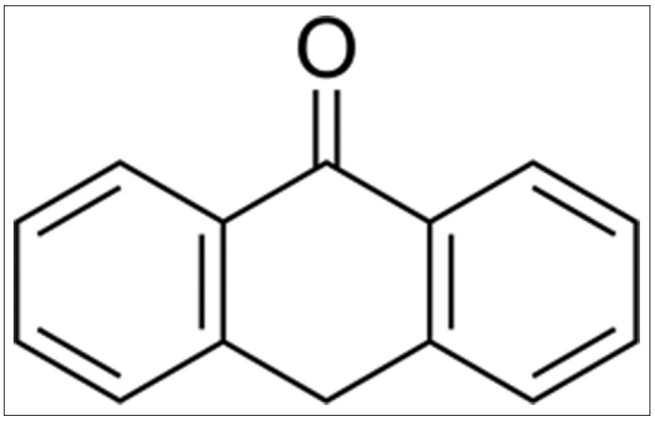


Figure 6: Chemical structure of anthrones

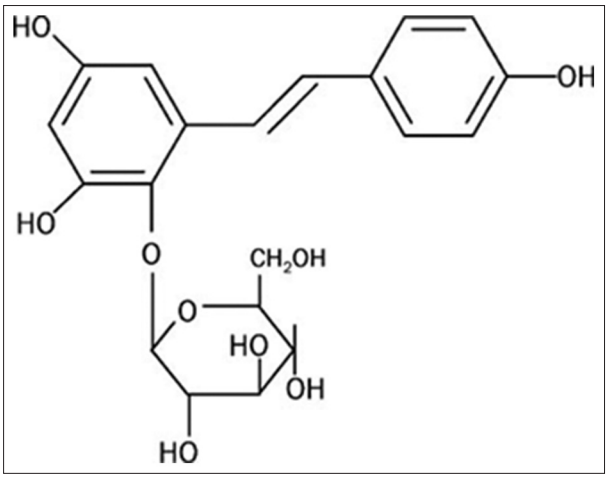


Figure 8: 2,3,5,4'-tetrahydroxylstilbene-2-O-β-D-glucoside

CLINICAL STUDIES DONE ON *POLYGONUM MULTIFLORUM* AND/OR ITS BIOACTIVE COMPOUNDS

In general, sound scientific evidence is lacking to support the use of many of the herbs currently marketed. A number of herbal products rely on anecdotal evidence to support their use. Many of the clinical trials in the literature are of limited quality owing to small sample sizes, improper randomization, and/or the lack of adequate controls. Large-scale, randomized, controlled trials have not been undertaken by the herbal industry owing to the fact that herbs are not patentable, and the potential of economic gain from positive study results is limited. A number of researchers and organizations (e.g. Cochrane collaboration) have attempted to critically evaluate available study data through systematic reviews and meta-analyses. Many of the analyses have been equivocal.[68] The use of herbal medicines presents unique clinical and pharmacological challenges not encountered with conventional single-compound medicines. These medicines are usually complex mixtures of many bioactive compounds and conventional "indications and uses" criteria devised for single-compound entities may not be applicable in a significant number of ways.[69]

Few clinical studies have been conducted to evaluate the traditional therapeutic claims and to study the potential of PMT and/or its various bioactive constituents, highlighting available clinical evidence.

Anti-inflammatory bioactivity

Inflammation is known to contribute to physiological and pathological processes by the activation of the immune system, local vascular system, and various cells within the damaged tissue.[70] Prolonged inflammation, known as chronic inflammation, is caused by a variety of factors, including microbial pathogen infection, physical, chemical, and surgical irritation, and/or wounding and it is involved in the pathogenesis of various many chronic diseases, including inflammatory bowel diseases, rheumatoid arthritis, sepsis, and cancer.[71-74] The classical characteristics of inflammation are pain, swelling, edema, redness, and heat.[75] Accumulating epidemiological, and clinical evidence shows that chronic inflammation is an important risk factor for various human diseases.[76] Therefore, suppressing the production of pro-inflammatory molecules and signaling factors is one of the important target pathways in order to prevent or treat various diseases.

Various natural products from TCM have been shown to safely suppress pro-inflammatory pathways and control inflammation-associated disease. *In vivo* and/or *in vitro* studies have demonstrated that anti-inflammatory effects of PMT and/or its bioactive constituents occur by inhibition of the expression of pro-inflammatory signaling factors such as nuclear factor-κB, tumor necrosis factor-α, inducible nitric oxide synthase, cyclooxygenase-2, chemokines (e.g.,: CCL2) and cytokines (e.g.: Interleukin-1 beta).[13,52,74,77] *P. multiflorum* was significantly tested for the treatment of the localized neurodermatitis by plum-blossom needle taping in a clinical study that enrolled 141 patients.[78] Moreover, STD07 (Physcion) developed by Sun Tem Phytotech for the treatment of inflammatory bowel diseases, was evaluated in a randomized, double-blind, single-centered and placebo controlled study in Asian healthy volunteers.[79] The authors found that up to 250 mg/day orally for 14 days; STD07 was general well tolerated with no clinically meaningful adverse effects in healthy volunteers in this Phase I clinical trial. Good therapeutic evidences of *P. multilforum* and/or its bioactive constituents have been shown in these aforementioned clinical studies to be used as anti-inflammatory agents. However, extensive clinical research is needed concerning the therapeutic value of this herbal medicine on its anti-inflammatory activity.

Dyslipidemia

The hepatocytes play important role in the distribution, biosynthesis, transferring and removal of triglyceride (TG), total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL) and other related lipoproteins.[80] In normal human liver, the mean contents of TC and TG are 3.9 and 19.5 mg/g wet weight, respectively. Traditionally, liver fat content >50 mg/g (5% by wet weight) is diagnostic of hepatic steatosis.[81] Dyslipidemia, defined as any abnormality of serum lipids and lipoproteins, including low levels of HDL-cholesterol that is associated with increased coronary heart diseases (CHD) risk, is a substantial contributor to the incidence of CHD.[37] In developed countries, most dyslipidemias are hyperlipidemias; that is, an elevation of lipids in the blood. This is often due to diet and lifestyle. Prolonged elevation of insulin levels can also lead to dyslipidemia. Similarly, increased levels of O-GlcNAc transferase may cause dyslipidemia. Dyslipidemia can be treated with dietary alterations and medications that affect lipid metabolism via a variety of mechanisms.[82] Being the first-line therapies for reducing LDL-C serum levels, statins also have adverse effects, including muscle myopathy and derangements in hepatic function.[83] Fibrates are second-line drugs that are used for the treatment of dyslipidemia and reduce serum TG levels by activating peroxisome proliferator-activated receptor alpha. However, fibrates increase serum creatinine concentrations[84] and have been correlated with sudden death, pancreatitis, and venous thrombosis.[85]

Traditional Chinese medicine plays a very important role in the treatment of dyslipidemic patients.[86] An early uncontrolled clinical study of 50 hyperlipidemic patients suggested that PMT has lipid-lowering effect which may be related to its regulatory effect on the genes involved in cholesterol synthesis and lipoprotein metabolism.[87] In a very recent randomized, double-blind, placebo-controlled clinical trial, the therapeutic effect of *P. multiflorum* in patients with dyslipidemia was investigated.[88] The findings concluded that being a considerable composition of the multiherb formula, *P. multiflorum* showed marginal beneficial effect on reducing plasma LDL cholesterol levels in patients with dyslipidemia. In order to validate the claimed dyslipidemia therapeutic action of *P. multiflorum* and/or its bioactive compounds, further well-designed clinical studies with solid evidence are warranted to investigate this mechanism.

Sleep disorders

Insomnia or sleeplessness is a sleep disorder in which there is an inability to fall asleep or to stay asleep as long as desired.[89] It is prevalent in woman and the elderly by 40% more common in women than in men.[90,91] Different measures, such as pharmacotherapy and behavioral management, are applied for insomnia and associated complaints.[92] Current insomnia pharmacotherapeutic agents mainly target the γ-aminobutyric acid (GABA) receptor, melatonin receptor, histamine receptor, orexin, and serotonin receptor. GABA receptor modulators are ordinarily used to manage insomnia, but they are known to affect sleep maintenance, including residual effects, tolerance, and dependence.[91] An analysis of the United States National Health Interview Survey data from 2002 by Pearson *et al*.[133] revealed that of the 17.4% of adults (n = 93 386) reporting insomnia or regular sleep disturbance in the preceding month, 4.5% (of that population) used complementary and alternative medicine to improve their sleep.

In an effort to discover new drugs that relieve insomnia symptoms while avoiding side effects, numerous studies focusing on the neurotransmitter GABA and herbal medicines have been conducted. Several traditional herbal medicines, such as *Valeriana officinalis*,[93,94] *Passiflora incarnata*,[95,96] *Matricaria recutita* L.,[97,98] *Humulus lupulus*,[99,100] *Ginkgo bibola*,[101] *Centella asiatica*,[102] *Rhodiola rosea*,[103] *Hypericum perforatum*,[104] *Piper methysticum*[105,106] and *Zizyphus jujuba*[14] have been widely clinically reported to improve sleep and other mental disorders. Moreover, recently Wuling capsule, a single herb formula from *mycelia of precious Xylaria nigripes* was investigated for its efficacy and safety, through a multicenter, randomized, double-blind, placebo-controlled trail, in Chinese patients with insomnia.[107] The clinical findings claimed that Wuling capsule could considerably improve insomnia and in terms of adverse effect, on a-6 weeks study period the drug was well-tolerated by all the patients.

In the first large-scale survey done in Taiwan of the use of Chinese herbal medicines (CHMs) or the treatment of insomnia in a Chinese population, *P. multiflorum* was found to be the most commonly prescribed single Chinese herb.[14] Furthermore, among the Chinese herbal formulas used to treat insomnia, *P. multiflorum* was found significantly an important constituent of the ingredients. Although Shou-wu-teng (*P. multiflorum*) is often used to treat insomnia during clinical practice, no clinical research exists in the Western literature verifying its sedative or anxiolytic effects.[14] Despite limited evidence from currently available studies, herbal medicines, especially *P. multiflorum* and/or its bioactive compounds may have beneficial effects on anxiety and insomnia in patients with bipolar disorder.[108]

Anti-insomniac phytotherapy opens up an exciting aspect of research which might benefit a large number of patients suffering from different degrees of insomnia. Future research using CHM for sleep disorders requires further rigorous studies with improved methodological design, such as using an appropriate placebo control, double-blinding, validated outcome scales, and longer follow-up periods.[109] There is a need for more PD and PK studies to examine the mechanism of action, dosage regimen, toxicology and adverse effects, if there are any drug interactions and the epigenetic differences affected between single active constituents versus whole extracts and complex prescriptive formulas.[109,110] In order to avoid location bias, as nearly all these studies are conducted in China, other countries are also encouraged further to pursue CHM clinical studies in the treatment of sleep disorders.[112]

Neurodegenerative disease

Age is the leading risk factor for acute and chronic neurodegenerative diseases such as Parkinson's disease (PD), stroke, Huntington's disease (HD), vascular dementia (VaD) and Alzheimer's disease (AD), etc., As population aging is occurring on a global scale, the incidence of these diseases is likely to increase significantly in the near future.[111] They show common pathology of aggregation and deposition of abnormal protein. For example, deposit of Aβ and tau in AD,[112] α-Synuclein for Parkinson's disease,[113] huntingtin protein in HD,[114] transactive response DNA-binding protein 43 in frontotemporal dementia and amyotrophic lateral sclerosis.[115] Neurodegenerative diseases usually have the symptoms of loss of orientation, spoken language, comprehension and learning abilities. To date, there is a lack of effective preventive strategies for these disorders. Furthermore, treatments are mainly symptomatic and can at best temporarily slow down disease progression.[111] Moreover, lack of treatment options has led to an increasing number of people to use "natural" and herbal medicines in an attempt to prevent or delay the deleterious effects

of ageing as longevity and good health have always been desirable goals for humans.

Various herbal medicines and/or their bioactive compounds have been found to exert significant therapeutic effect *in vitro* model of neurodegenerative diseases. Pharmacological studies of PMT extract claimed that this medicinal plant may be beneficial in preventing PD[31] and AD.[9] Furthermore, TSG [Figure 8], one of the bioactive compounds purified from its roots significantly antagonized age-related α-synuclein overexpression in the hippocampus of APP transgenic mouse model of AD[116] and possessed neuroprotection in the 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of Parkinson's disease.[35] *Ginkgo biloba* and *Lycopodium serratum* (Huperzine A), through various randomized, double-blind, placebo-controlled, parallel and multi-center clinical trials have been assessed for their clinical efficacy and safety in AD treatment.[117,118] Their claimed neuroprotective therapeutic activity was significantly expressed on mild AD clinical cases.

Few clinical trials have investigated the potential therapeutic activity of PMT in neurodegenerative diseases. Chen *et al.* observed the clinical effect of PMT extract on AD.[119] The findings suggested that the scores for the Mini-Mental State Examination and the Ability of Daily Living Scale were significantly improved in the treatment group compared to the Chinese herb control group and the western medicine control group ($P < 0.01$). Moreover, in a randomized, Piracetam-controlled, single-center clinical trial, *P. multiflorum* (Shouwu yizhi capsule) was evaluated as monotherapy for VaD.[120] The authors found that the total clinical effective rate was 71.25% and that the herbal medicinal had obvious therapeutic effect on VaD, with no relative adverse drug reactions.

DCB-AD1 is a new drug derived from PMT and a medical team in Taiwan is proposing a Phase II double-blind, randomized, placebo-controlled and parallel clinical trial to assess its efficacy and safety in patients with mild to moderate AD.[121] We therefore believe that further high quality clinical studies on PMT and its isolated bio-compounds, as well as the herbal mixtures resulted, will assess its actual clinical value and could lead to the discovery of new drugs for effective treatment and prevention of neurodegenerative diseases.

CLINICAL CASES OF *POLYGONUM MULTIFLORUM*-INDUCED HEPATOTOXICITY

Herbal medicines are generally sold as food supplements, and as a consequence, therapeutic indications, efficacy, and safety are influenced by different opinions, according to the clinical or traditional experience of various folk medicines available in each country.[122] The market regulation of herbal medicines is not harmonized because there are different regulations in European, Asian and North American countries, and as a consequence, this lack of rules gives poor guarantee of clinical safety.[123] Many herbal products have been shown to cause severe toxicity, but, despite the potential toxicity, there is widespread use among eastern and western general population. Information on clinical issues of herbal medicines are scarcely available and even if they have been reported, unlike what happens general practitioners may not be fully informed since correct use and safety of herbal medicinal products is not taught by academic institutions in medicine faculties.[124] The current situation requires the knowledge, recognition and monitoring of adverse reactions through pharmacovigilance activities.

Herbal hepatotoxicity or herb-induced liver injury is rare and represents a bundle of disorders, each characterized by a specific herb or herbal mixture considered as potentially hepatotoxic.[125] Any individual herb with its multiple chemical constituents may target different liver cell types and/or different subcellular structures, causing likely different diagnostic markers for potentially hepatotoxic herbs and injury types with no single marker characteristic for herbal liver damage.[126] *P. multiflorum* (Shou-Wu-Pian and Shen-Min have been the most-well known products), being one of the most famous Chinese herbs to treat several diseases and medical conditions including dizziness with tinnitus, premature greying of hair, lumbago, spermatorrhea, leucorrhea, constipation and even chronic hepatitis B,[38,59,127] has also been ranked in the top five of individual herbs or used most frequently in TCM formulations to induce hepatotoxicity.[128] Several cases of hepatotoxicity due to PMT have been reported in patients from Australia, China, Italy, Japan, The Netherlands and Slovakia taking the product for hair loss, chronic prostatitis and to boost the immune system.[38-40,58,60,129]

The patients had a history of having ingested PMT in various forms (tea boil with PMT, liquor made of PMT, honey-soaked out with PMT, and the powder of dried PMT). However, it raised the issue concerning the form of the intake with the relation to the severity of hepatotoxicity.[59] The processed roots of PMT have displayed lower rates of toxicity as reported in animal experiments.[130] Processing appears to significantly reduce the amount of chemicals like 2,3,4′5-tetrahydroxystilbene-2-O-β-Dglucoside, but it remains to be determined if this can explain reduced toxicity in humans. For raw PMT, the toxicity of water decocta appears to be higher than that of

acetone extract. Meanwhile, the toxicity of acetone extract of unprocessed PMT is considerably higher than that of acetone extract of processed PMT. High-performance liquid chromatography analyses and nuclear magnetic resonance analysis revealed that the contents of characteristic compounds in raw PMT were changed after processing: The content of 2,3,4′,5-tetrahydroxystilbene 2-O-β-D-glucoside was decreased by 55.8%, whereas the content of anthraquinone emodin was increased by 34.0%.[40,130] Thus, suggesting that processing should reduce the toxicity of *P. multiflorum*.

CONCLUSION

Plants have been selected and use empirically as drugs for centuries, initially as traditional preparations then as pure active principles, with the knowledge and accumulated practice passing from generation to generation.[1] Herbal medicine, phytotherapy, phytomedicine, complementary and alternative medicine, ethnomedicine, herbal medicinal product and dietary supplements are all terms used interchangeably to denote the use of botanicals in healthcare and are therefore used as such in this text.[131] The human population is a total mixture, unlike selected batches of laboratory animals (same age, weight, sex, strain, etc.). For this reason, human beings do not respond uniformly to one or more drugs or even herbal medicines. Our genetic make-up, ethnic background, sex, renal and hepatic functions, diseases and nutritional states, ages and other factors such as the route of administration, all contribute toward the heterogeneity of our responses.[132]

Pharmacological studies have demonstrated that PMT. extracts and/or its isolated pure compound possessed various biological activities such as anti-bacterial, anti-inflammatory, anti-diabetic, anti-cancer, anti-oxidant and exerting preventing activity against neurodegenerative diseases as well. Clinical investigations have enlightened its claimed therapeutic action in anti-inflammatory, dyslipidemia, sleep disorders and neurodegenerative diseases. A general lack of knowledge of the interaction potentials of concurrent use of herbal medicines with prescription and/or over-the counter medicines poses a great challenge for health care professional and safety concern for the patients. In the recent years, due to increasing reports of herbal-induced hepatotoxicity, the clinical efficacy and safety of *P. multiflorum* and/or its isolated compounds have attracted much interest. The clinical presentation and severity of *P. multiflorum* can be highly variable, ranging from mild hepatitis to acute hepatitis failure requiring transplantation.

Pharmacists and technicians, as well as physicians, dieticians, and other health care providers must become knowledgeable about herbal supplements and prospectively seek information regarding their patients' use of unconventional medicines to avoid adverse consequences. Consumers need to be reminded that herbs are composed of chemicals that may, in some cases be toxic, especially if large quantities are ingested. Furthermore, much developed countries and scientific societies are encouraged to conduct clinical studies on *P. multiflorum* and/or its isolated compounds in order to evaluate their claimed therapeutic activities.

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