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.

Key words: Clinical pharmacokinetics, clinical studies, herbal hepatotoxicity, Polygonum multiflorum Thunb., therapeutic assessment

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,[6] is one of the most popular perennial Chinese traditional medicinal vine-like herbs, officially listed in the Chinese Pharmacopoeia.[8] 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,[19] anti-oxidant,[19-21] anti-HIV,[22] liver protection,[23,24] nephroprotection,[25] antidiabetic,[13,26] anti-aloepecia,[27,28] and anti-atherosclerotic activities.[29,30] It has been also reported to exert preventive activity against neurodegenerative diseases,[31-33] 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...
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

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**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 is 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-gp[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 sparse. 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  | CH₂OH|
| Chrysophanol | H  | CH₃  |
| Danthron     | H  | H    |
| Emodin       | OH | CH₃  |
| Physcion     | OCH₃| CH₃ |
| Rhein        | H  | COOH |

**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)

**Figure 4:** Chemical structures of aloe-emodin, chrysophanol, danthron, emodin, physcion and rhein
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).\textsuperscript{[53,63]} Li et al. investigated the inhibitory effect of PMT constituents on P-gp mediated the digoxin transport in MDR1-MDCKII cells. The herbal constituents tested were trans-Resveratrol [Figure 7], 2,3,5,4’-tetrahydroxyxylstilbene-2-O-β-D-glucoside (TSG, Figure 8), emodin, chrysophanol, aloe-emodin, and physcion. Among the various constituents of \textit{P. multiflorum} tested, emodin was significantly the strongest inhibitor of P-gp (IC$_{50}$ = 9.42 μM) in MDR1-MDCKII and Caco-2 cells.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[44,64]} CYP450 1A2 (CYP1A2) and CYP450 3A4 (CYP3A4) are involved in the metabolism of xenobiotic in the body,\textsuperscript{[65,66]} their expression appear to be induced by various herbal medicines and/or dietary constituents.\textsuperscript{[67]} The genotype and the allelic frequencies of CYP1A2 were evaluated in Chinese patients with acute liver injury induced by \textit{P. multiflorum} in order to investigate CYP1A2 allele polymorphism association with the hepatotoxicity from PMT.\textsuperscript{[55]} The findings revealed that the frequency of the CYP1A2 *1C mutation in Chinese patients with \textit{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.\textsuperscript{[55]} Moreover, despite the structural similarity and/or identical molecular weight of various herbal constituents, emodin significant inhibited CYP3A4/5 activity.\textsuperscript{[53]} Considering \textit{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.
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.\(^6^8\) 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.\(^6^9\)

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.\(^7^0\) 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.\(^7^1_u\) The classical characteristics of inflammation are pain, swelling, edema, redness, and heat.\(^7^9\) Accumulating epidemiological, and clinical evidence shows that chronic inflammation is an important risk factor for various human diseases.\(^7^0\) 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. \(^in\) \(v\)\(i\)\(t\) \(o\) \(v\) 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-\(\kappa\)B, tumor necrosis factor-\(\alpha\), inducible nitric oxide synthase, cyclooxygenase-2, chemokines (e.g., CCL2) and cytokines (e.g., Interleukin-1 beta).\(^1^3,5^2,7^4,7^7\) \(P.\ \)multiflorum was significantly tested for the treatment of the localized neurodermatitis by plum-blossom needle tapering in a clinical study that enrolled 141 patients.\(^7^8\) Moreover, STD07 (Physcione) 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.\(^7^9\) 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 \(P.\ \)multiflorum 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.\(^8^0\) 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.\(^8^1\) 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.\(^5^7\) 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.\(^8^2\) Being the first-line therapies for reducing LDL-C serum levels, statins also have adverse effects, including muscle myopathy and derangements in hepatic function.\(^8^3\) 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 and have been correlated with sudden death, pancreatitis, and venous thrombosis.\(^8^5\)
Traditional Chinese medicine plays a very important role in the treatment of dyslipidemic patients. 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. In a very recent randomized, double-blind, placebo-controlled clinical trial, the therapeutic effect of P. multiflorum in patients with dyslipidemia was investigated. The findings concluded that being a considerable composition of the multitherb 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. It is prevalent in woman and the elderly by 40% more common in women than in men. Different measures, such as pharmacotherapy and behavioral management, are applied for insomnia and associated complaints. 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. An analysis of the United States National Health Interview Survey data from 2002 by Pearson et al. 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, Passiflora incarnata, Matricaria recutita L., Humulus lupulus, Ginkgo biloba, Centella asiatica, Rhodolia rosea, Hypericum perforatum, Piper methysticum, and Ziziphus jujuba 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 trial, in Chinese patients with insomnia. 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. Furthermore, among the Chinese herbal formulas used to treat insomnia, P. multiflorum was found significantly an important constituent of the ingredients. Though 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. 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.

Anti-insomniac phyotherapy 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. 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. 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.

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. They show common pathology of aggregation and deposition of abnormal protein. For example, deposit of Aβ and tau in AD, α-Synuclein for Parkinson’s disease, huntingtin protein in HD, transactive response DNA-binding protein 43 in frontotemporal dementia and amyotrophic lateral sclerosis. 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. 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.
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 and AD. 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 and possessed neuroprotection in the 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of Parkinson’s disease. 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. 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. 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. 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. 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. 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. 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. 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. 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. 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, leucorrhrea, constipation and even chronic hepatitis B has also been ranked in the top five of individual herbs or used most frequently in TCM formulations to induce hepatotoxicity. 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.

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. The processed roots of PMT have displayed lower rates of toxicity as reported in animal experiments. Processing appears to significantly reduce the amount of chemicals like 2,3,4′,5′-tetrahydroxystilbene-2-O-β-D-glucoside, 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%. Thus, suggesting that processing should reduce the toxicity of *P. multiflorum*.

**CONCLUSION**

Plants 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. 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. 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.

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.

**REFERENCES**

1. Taylor JL, Rabe T, McGrav L, Jäger AK, van Staden J. Towards the scientific validation of traditional medicinal plants. Plant Growth Regul 2001; 34:23-37.

2. Wachtel-Galor S, Benzie IF, editors. Herbal medicine: An introduction to its history, usage, regulation, current trends, and research needs. In: Herbal Medicine: Biomedical and Clinical Aspect. 2nd ed. Florida: CRC Press; 2011. p. 1-10.

3. Abolaji OA, Adebayo AH, Odesanmi OS. Nutritional qualities of three medicinal plants parts (*Xylopia aethiopica, Blighia sapida* and *Parinari polypandra*) commonly used by pregnant women in the western part of Nigeria. Pak J Nutr 2007; 6:655-45.

4. Hamburger M, Hostettman K. Bioactivity in plants: The link between phytochemistry and medicine. Phytochemistry 1991; 30:3864-74.

5. Lu L, Shao X, Wang L, Huang D, Ho CT, Sang S. Stilbene glucoside from *Polygonum multiflorum* Thunb.: A novel natural inhibitor of advanced glycation end product formation by trapping of methylglyoxal. J Agric Food Chem 2010; 58:2239-45.

6. Pharmacopoeia Commission of the Ministry of Health, Pharmacopoeia of the People’s Republic of China (PPRC). 1st Div. Beijing: China Chemical Industry Press; 2010. p. 22-3.

7. Grech JN, Li Q, Roufogalis BD, Duck CC. Novel Ca(2+)–ATPase inhibitors from the dried root tubers of *Polygonum Multiflorum*. J Nat Prod 1994;57:1682-7.

8. Kam JK. Mutagenic activity of Ho Shao Wu (*Polygonum multiflorum* Thunb). Am J Chin Med 1981; 9:213-5.

9. Um MY, Choi WH, Aan JY, Kim SR, Ha TY. Protective effect of *Polygonum multiflorum* Thunb on amyloid beta-peptide 25-35 induced cognitive deficits in mice. J Ethnopharmacol 2006; 104:144-8.

10. Kwon BM, Kim SH, Baek NI, Lee SI, Kim EJ, Yang JH, et al. Farnesyl protein transferase inhibitory components of *Polygonum multiflorum*. Arch Pharm Res 2009; 32:495-9.

11. Yang LJ. Insussuction on the application of hair-blackening and hair growth accelerating effects of *Polygonum multiflorum* from ancient prescription. J Tradit Chin Med 2008; 7:39-40.

12. Guan S, Su W, Wang N, Li P, Wang Y. Effects of radix polgyoni multiflori components on tyrosinase activity and melanogenesis. J Enzyme Inhib Med Chem 2008; 23:252-5.

13. Cha DS, Jeon H. Anti-inflammatory effect of MeOH extracts of the stem of *Polygonum multiflorum* in LPS-stimulated mouse peritoneal macrophages. Nat Prod Sci 2009;15:83-9.

14. Chen FP, Jong MS, Chen YC, Kung YY, Chen TJ, Chen FJ, et al. Prescriptions of Chinese herbal medicines for insomnia in Taiwan during 2002. Evid Based Complement Alternat Med 2011;2011:236341.
50. Zhu W, Wang XM, Zhang L, Li XY, Wang BX. Pharmacokinetic of rhein in healthy male volunteers following oral and retention enema administration of rhubarb extract: A single dose study. Am J Chin Med 2005;33:839-50.

51. Zhang B, Shi Y, Lei TC. Detection of active P-glycoprotein in systemic lupus erythematosus patients with poor disease control. Exp Ther Med 2012;4:705-10.

52. Choi RJ, Ngoc TM, Bae K, Cho HJ, Kim DD, Chun J, et al. Anti-inflammatory properties of anthraquinones and their relationship with the regulation of P-glycoprotein function and expression. Eur J Pharm Sci 2013;48:272-81.

53. Li X, Hu J, Wang B, Sheng L, Liu Z, Yang S, et al. Inhibitory effects of herbal constituents on P-glycoprotein in vitro and in vivo: Herb-drug interactions mediated via P-gp. Toxicol Appl Pharmacol 2014;275:163-75.

54. Unger M, Frank A. Simultaneous determination of the inhibitory potency of herbal extracts on the activity of six major cytochrome P450 enzymes using liquid chromatography/mass spectrometry and automated online extraction. Rapid Commun Mass Spectrom 2004;18:2273-81.

55. Ma KF, Zhang XG, Jia HY. CYP1A2 polymorphism in Chinese patients with acute liver injury induced by Polygonum multiflorum. Genet Mol Res 2014;13:5637-43.

56. But PP, Tomlinson B, Lee KL. Hepatitis related to the Chinese medicine Shou-wu-pian manufactured from Polygonum multiflorum. Vet Hum Toxicol 1996;38:280-2.

57. Yuen MF, Tam S, Fung J, Wong DK, Wong BC, Lai CL. Traditional Chinese medicine causing hepatotoxicity in patients with chronic hepatitis B infection: A 1-year prospective study. Aliment Pharmacol Ther 2006;24:1179-86.

58. Furukawa M, Kasajima S, Nakamura Y, Shouzushima M, Nagatani N, Takinashi A, et al. Toxic hepatitis induced by shou-wu-pian, a Chinese herbal preparation. Intern Med 2010;49:1537-40.

59. Jung KA, Min HJ, Yoo SS, Kim HJ, Choi SN, Ha CY, et al. Drug-induced liver injury: Twenty five cases of acute hepatitis following ingestion of Polygonum multiflorum Thunb. Gut Liver 2011;5:493-9.

60. Dong H, Slain D, Cheng J, Ma W, Liang W. Eighteen cases of liver injury following ingestion of Polygonum multiflorum. Complement Ther Med 2014;22:70-4.

61. Thiebaut F, Tsuruo T, Hamada H, Gottesman MM, Pastan I, Willingham MC. Cellular localization of the multidrug-resistance gene product P-glycoprotein in normal human tissues. Proc Natl Acad Sci U S A 1987;84:7735-8.

62. Izzo AA, Ernst E. Interactions between herbal medicines and prescribed drugs: A systematic review. Drugs 2001;61:2163-75.

63. Dür D, Steger B, Kullak-Ublick GA, Rentsch HC, Meier PJ, et al. St John’s Wort induces intestinal P-glycoprotein/MDR1 and intestinal and hepatic CYP3A4. Clin Pharmacol Ther 2000;68:598-604.

64. Sekine I, Saijo N. Polymorphisms of metabolizing enzymes and transporter proteins involved in the clearance of anticancer agents. Ann Oncol 2001;12:1515-25.

65. Gibbs MA, Thummel KE, Shen DD, Kunze KL. Inhibition of cytochrome P-450 3A (CYP3A) in human intestinal and liver microsomes: Comparison of Ki values and impact of CYP3A5 expression. Drug Metab Dispos 1999;27:180-7.

66. Nelson DR, Zeldin DC, Hoffman SM, Maltais LJ, Wain HM, Nebert DW. Comparison of cytochrome P450 (CYP) genes from the mouse and human genomes, including nomenclature recommendations for genes, pseudogenes and alternative-splice variants. Pharmacogenomics 2004;14:1-18.

67. Fontana RJ, Lown KS, Paine MF, Fortlage L, Santella RM, Felton JS, et al. Effects of a chargrilled meat diet on expression of CYP3A, CYP1A, and P-glycoprotein levels in healthy volunteers. Gastroenterology 1999;117:89-98.

68. Ashar BH, Dobs AS. Clinical trials for herbal extracts. In: Packer L, Ong CN, Halliwell B, editors. Herbal and Traditional Medicine: Molecular Aspect of Health. New York: Marcel Dekker; 2004. p. 53-72.

69. Yong EL, Loh YS. Herbal medicines: Criteria for use in health and disease. In: Packer L, Ong CN, Halliwell B, editors. Herbal and Traditional Medicine: Molecular Aspect of Health. New York: Marcel Dekker; 2004. p. 73-86.

70. Coussens LM, Werb Z. Inflammation and cancer. Nature 2002;420:860-7.

71. Ljung T, Lundberg S, Varsanyi M, Johansson C, Schmidt PT, Herulf M, et al. Rectal nitric oxide as biomarker in the treatment of inflammatory bowel disease: Responders versus nonresponders. World J Gastroenterol 2006;12:3386-92.

72. Park MY, Kwon HJ, Sung MK. Evaluation of aloin and aloen-edomin as anti-inflammatory agents in aloe by using murine macrophages. Biosci Biotechnol Biochem 2009;73:828-32.

73. Moore KJ, Tabas I. Macrophages in the pathogenesis of atherosclerosis. Cell 2011;145:341-55.

74. Pan MH, Chiuw YS, Tsai ML, Ho CT. Anti-inflammatory activity of traditional Chinese medicinal herbs. J Tradit Complement Med 2011;1:8-24.

75. Mantovani A. Molecular pathways linking inflammation and cancer. Curr Mol Med 2010;10:369-73.

76. Khatami M. Inflammation, aging, and cancer: Tumoricidal versus tumorigenesis of immunity: A common denominator mapping chronic diseases. Cell Biochem Biophys 2009;55:55-79.

77. Meng G, Liu Y, Lou C, Yang H. Emodin suppresses lipopolysaccharide-induced pro-inflammatory responses and NF-kB activation by disrupting lipid rafts in CD14-negative endothelial cells. Br J Pharmacol 2010;161:1628-44.

78. Weiying L, Yuanjiang D, Baolian L. Treatment of the localized neurodermatitis by plum-blossom needle tapping and with the modified yangxue dingfeng tang -- A clinical observation of 47 cases. J Tradit Chin Med 2006;26:181-3.

79. Tzeng TB, Chang WK, Huang TY, Wu PT, Huang WC, Lee C, et al. Safety and tolerability of physcion in healthy volunteers in a phase I dose escalating clinical pharmacology study. Gastroenterology 2011;140:8572.

80. Wang M, Zhao R, Wang W, Mao X, Yu J. Lipid regulation effects of Polygoni multiflori Radix, its processed products and its major substances on steatosis human liver cell line LO2. J Ethnopharmacol 2012;139:287-93.

81. Szczepaniak LS, Nurenberg P, Leonard D, Browing JD, Reingold JS, Grundy S, et al. Magnetic resonance spectroscopy to measure hepatic triglyceride content: Prevalence of hepatic steatosis in the general population. Am J Physiol Endocrinol Metab 2005;288:E462-8.

82. Toth PP. Drug treatment of hyperlipidaemia: A guide to the rational use of lipid-lowering drugs. Drugs 2010;70:1363-79.

83. Maggo SD, Kennedy MA, Clark DW. Clinical implications of pharmacogenetic variation on the effects of statins. Drug Saf 2011;34:1-19.

84. Jun M, Foote C, Lv J, Neal B, Patel A, Nicholls SJ, et al. Effects of fibrates on cardiovascular outcomes: A systematic review and meta-analysis. Lancet 2010;375:1875-84.

85. Wierzbicki AS. Fibrates in the treatment of cardiovascular risk and atherogenic dyslipidaemia. Curr Opin Cardiol 2009;24:372-9.

86. Dou XB, Wo XD, Fan CL. Progress of research in treatment of hyperlipidemia by monomer or compound recipe of Chinese herbal medicine. Chin J Integr Med 2008;14:71-5.
125. Teschke R, Wolff A, Frenzel C, Schulze J, Eickhoff A. Herbal hepatotoxicity: A tabular compilation of reported cases. Liver Int 2012;32:1543-56.
126. Teschke R, Genthner A, Wolff A, Frenzel C, Schulze J, Eickhoff A. Herbal hepatotoxicity: Analysis of cases with initially reported positive re-exposure tests. Dig Liver Dis 2014;46:264-9.
127. Laird AR, Ramchandani N, deGoma EM, Avula B, Khan IA, Gesundheit N. Acute hepatitis associated with the use of an herbal supplement (Polygonum multiflorum) mimicking iron-overload syndrome. J Clin Gastroenterol 2008;42:861-2.
128. Wang GQ, Deng YQ, Hou FQ. Overview of drug-induced liver injury in China. Clin Liver Dis 2014;4:26-9.
129. Banarova A, Koller T, Payer J. Toxic hepatitis induced by Polygonum multiflorum. Vnitr Lek 2012;58:958-62.
130. Wu X, Chen X, Huang Q, Fang D, Li G, Zhang G. Toxicity of raw and processed roots of Polygonum multiflorum. Fitoterapia 2012;83:469-75.
131. Obodozie OO. Pharmacokinetics and drug interactions of herbal medicines: A missing critical step in the phytomedicine/drug development process. In: Noreddin A, editor. Reading in Advanced Pharmacokinetics – Theory, Methods, and Applications. Croatia: InTech; 2012. p. 127-56.
132. Williamson E, Driver S, Baxter K. Stockley’s Herbal Medicines Interactions. London: Pharmaceutical Press; 2009. p. 1-10.
133. Pearson NJ, Johnson LL, Nahin RL. Insomnia, trouble sleeping, and complementary and alternative medicine: Analysis of the 2002 national health interview survey data. Arch Intern Med 2006;166:1775-82.

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