



Traditional Use and Safety of Herbal Medicines

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Traditional or folk medicine

Traditional or folk medicine comprises practices, approaches, knowledge and beliefs not based on scientific evidence that are applied to treat, diagnose and prevent illness within a society

It is defined by a culture's knowledge and values and thus is context-specific, as are social constructions and negotiations of risk

However, there is limited scientific evidence to establish the safety and efficacy of most herbal products

In recent decades, spectrum of disease has shifted and the complex chronic diseases have become the main part

The effect of Western medicine treatment is not satisfactory and problems of the adverse drug reaction are also very prominent

The complementary and alternative treatment, especially the herbal medicine, has gained more attention and has also become popular

About 100 years ago, natural herbs were the main remedy for treating human diseases

It has been estimated that 25% of modern medicines are made from plants first used traditionally

For example aspirin, artemisinin, ephedrine, and paclitaxel

In 2019, the global market for herbal remedies was about USD 150 billion

In China, the industry output value of Chinese patent medicines reached about USD 80 billion in 2018

Safety Issues of Herbal Medicine

Along with the significant increase of worldwide consumption, the safety of herbal medicine has been highlighted

At present, there are misunderstanding and prejudice toward the safety of herbal medicine

So, objective understanding, neutral and fair interpretation, and publicity are warranted

(a) Herbal Medicine Is Drug, Not Food

Advocates will advertise that herbal medicine originated from nature and belongs to green therapy and has no toxin or adverse effect and people can take it in the long term and so forth

These sayings are slogans of the advocates which have misled people with less medical knowledge

On one hand, it will lead to many severe adverse events by misusing herbal medicine;

On the other hand, it will cause people's panic and anxiety due to some adverse events reports

We should clearly recognize that herbal medicinal products are widely considered to be of lower risk compared with synthetic drugs

They are not completely free from the possibility of toxicity or adverse effects

Exaggerated propaganda and giving up using for adverse event are prejudice against herbal medicine

Therefore, to ensure the safety use of herbal medicinal products, herbal medicine should be managed as drug.

(b) Relative Property of Herbal Medicine Safety

As the Chinese saying goes, “all medicines have their own side effects”; that is, medicine is a double-blade sword

It can cure disease or maintain health, while it may also cause damage to human body

All effective drugs may produce adverse drug reactions; herbal medicines are no exception

Over dosage and course of treatment are bound to safety problems

For Example

The toxicity of *Radix Bupleuri Chinensis* in Japan has attracted worldwide attentions

A research on the quantity-toxin relation indicates that the toxic dose of *Radix Bupleuri Chinensis* (192 g/60 kg) is much greater than clinical common dose (9 g/60 kg)

However, high-dose and long-term use may also cause adverse event

(c) Complexity of Safety of Herbal Medicine

There are a number of causes of adverse events to herbal medicines, which can be divided into “direct” and “indirect” reasons

Intrinsic Toxicity

Direct reason is the intrinsic toxicity of some herb at normal therapeutic dosage or in overdose

Adverse reactions associated with *Ephedra*, *Aristolochia*, and *Aconitum* have shown that herbs can produce toxicity in humans

External Toxicity

Adverse effects associated with herbal medicines may result from contamination of products with toxic metals, adulteration, misidentification or substitution of herbal ingredients, or improperly processed or prepared products

For example, *Caulis Akebiae* replaced by *Caulis Aristolochiae Manshuriensis* and *Stephania tetrandra* replaced by *Aristolochia fangchi* have led to the serious problem of “aristolochic acid nephropathy

Wrong Indication

Inappropriate use of herbal medicines can cause negative or dangerous effects

For instance, the herb Ephedra is traditionally used in China to treat respiratory congestion,

While it was marketed as dietary supplements formulated for weight reduction in US.

Over dosage led to at least a dozen deaths, heart attacks, and strokes

Herb-Drug Interaction

All herbal medicines are complex mixtures of more than one active ingredient

Multitude of active ingredients will increase the possibilities of interactions b/w herbal medicines and conventional drugs

Moreover, users of medicinal herbs are usually suffering from chronic conditions for which they are likely to take prescribed drugs concomitantly

This, in turn, further increases the potential of herb-drug interaction

Herbal medicine regimens containing *Radix Bupleuri*, *Fructus Gardenia*, *Fructus Schisandrae Chinensis*, *Radix Rehmanniae*, *Akebia Caulis*, and *Semen Plantaginis* in concomitant use with quetiapine, clozapine, and olanzapine

were associated with nearly 60% of the risk of adverse outcomes

(d) Weak Basic Research in Safety of Herbal Medicine

Efficacy and toxicity of the majority of herbal medicine are mostly based on traditional knowledge and clinical experience

The toxicity classification is lack of scientific standard and objective experimental data

There is no adequate data about toxic herbs, toxic target organs, safe dose range, safety window of effective dose, and minimum toxic dose

Thus, to specify the toxic and adverse effect of each herbal medicine is a vital base to ensure the safe use of herbal medicine

Processing of herbal slices is an important step to decrease toxicity

For example, Heating processing can make the bitter almond enzyme lose activity and then decrease the toxicity of almond which contains cyanophoric glycoside

Diester-diterpenoid *Aconitum* Alkaloids are the strongest toxicity constituents of aconite and monkshood

By heating processing, diester-diterpenoid *Aconitum* Alkaloids can be decomposed into low toxicity monoester-diterpenoid *Alkaloids* and aconine which are of low toxicity and almost not toxic

Compatibility, which aims to decrease toxicity and improve treating effect for prescription, is the key theory of Chinese herbal medicine

For instance, combining *Radix aconiti praeparata* with licorice, *Aconitum* Alkaloids can decrease obviously
Ginger can antagonize the toxicity of *Rhizoma Pinelliae*

Therefore, the scientific connotation of compatibility and preparation of herbal medicine should be investigated deeply

Carcinogenic effects of traditional herbal medicines

Examples of traditional herbal medicines and/or their constituents with suspected carcinogenic effects.

Plant species	Constituent	Traditional use	Evidence		Reference
			Humans or animals	Findings	
<i>Aristolochia</i> sp.	Aristolochic acid (AA)	Chinese traditional medicine; arthritis, rheumatism, hepatitis, other indications.	Human	Nephrotoxicity, upper tract urothelial carcinoma; meta-analysis: OR = 5.97 (95% CI, 2.78-12.84) for AA-related cancers; TP53 mutations.	Chen et al., 2013; Hollstein et al., 2013; Wu and Wang, 2013.
<i>Thuja</i> sp., <i>Artemisia</i> sp., <i>Salvia officinalis</i> L.	α - β -thujone (essential oils)	Traditional medicine, flavoring food additives, absinthe (liqueur).	Rodents	Inhibitor of GABA-A receptor, seizures. Preputial gland and adrenal gland tumors in male rats (no treatment-related tumors in female rats and mice).	Halicioglu et al., 2011; NTP, 2011a, Pelkonen et al., 2013.
<i>Mentha</i> \times <i>piperita</i> L., <i>M. longifolia</i> (L.) Huds., <i>Nepeta cataria</i> L.	Peppermint and pennyroyal oils; pulegone	Traditional medicine, flavoring food additives.	Rodents	Hyaline glomerulopathy (male, female, mice, rats); Urinary bladder neoplasms (female rats), hepatocellular neoplasms (mice), osteoma/osteosarcoma (female mice), no tumors in male rats.	NTP, 2011b
<i>Sassafras albidum</i> (Nutt.) Nees, <i>Areca catechu</i> L., <i>Piper betle</i> L.	Sassafras oil; safrole	Traditional medicine, Native Americans and the British, betel quid chewing in Asia.	Human Rodents	Oral squamous carcinomas (humans), hepatocellular carcinomas; DNA-adduct formation and potent rodent carcinogen.	Amarasinghe et al., 2010; Chen et al., 1999; Hsieh et al., 2001; Kapadia et al., 1978; Liu et al., 2000.
<i>Pteridium</i> sp. (braken), ferns and lycopods	Sesquiterpenoids and analogues; ptaquiloside	Food (East Asia and American Indians), food and traditional medicine (New Zealand, the Maoris).	Human Rodents Cattle in vitro	Stomach and upper alimentary tract cancers, urinary bladder cancer, neoplasia of several tissues (rodents), thiamine deficiency, acute haemorrhage associated with myeloid aplasia, blindness and	Alonso-Amelot and Avendaño, 2002; Potter and Baird, 2000; Shahin et al., 1999; Tomšík, 2013.

<i>Symphytum officinale</i> L. (comfrey)	Pyrrrolizidine alkaloids	Traditional medicine, Africa, China, Ayurveda, and others.	Human Rodents	Hepatotoxicity, hepatic venous occlusive disease, liver cancer, genotoxicity, DNA adducts.	Chen et al., 2010; Mei et al., 2011; Roeder, 2000; Roeder and Wiedenfeld, 2011; 2013; Steenkamp et al., 2000.
<i>Euphorbia tirucalli</i> L.	Phorbol esters	Traditional medicine, Africa.	Human Rodents	Burkitt's lymphoma after co-exposure <i>E. tirucalli</i> + Epstein Barr virus, known tumor promoting agent in rodents. Dose-related increase in liver tumors including hepatocellular carcinoma (B6C3F1 mice). Evidence of carcinogenic potential in the thyroid gland (rats, mice); mutagenic (<i>S. typhimurium</i> TA98, TA100, <i>E. coli</i> WPS uvrA/pkM 101, with and without S9).	Aya et al., 1991; Imai et al., 1994.
<i>Gingko biloba</i> L.	Leaf extract	Chinese traditional medicine, widespread use worldwide.	Human Rodents	☒ liver and kidney malign tumors and DNA adducts, in male and female rats. Mutagenic in <i>S. typhimurium</i> TA 100 and TA 98 assay, V79 HGPRT assay, malignant transformation assay with C3H/M2 cells.	Hoenerhoff et al., 2013; NTP, 2013.
<i>Rubia tinctorum</i> L. (madder root)	Hydroxyanthraquinones, lucidin	Traditional medicine and dye. Ayurveda, and in Europe for kidney stones.	Rodents in vitro		Blömeke et al., 1992, Westendorf et al., 1988; 1998, Yasui and Takeda, 1983.
<i>Senna alata</i> L. (Roxb)	Sennosides	Traditional medicine (Africa, Nigeria, Ghana, Guinea).	Rodents in vitro	Mutagenic to <i>S. typhimurium</i> TA98 and TA 1537 with S-9.	Hong and Lyu, 2011.
Mixture of plants called Imbiza ephuzwato, Stameta™ BODicare®	(?)	Traditional medicine multi-purpose remedies and tonics (South Africa, The Zulu).	in vitro	Plant mixtures were mutagenic in <i>S. typhimurium</i> TA 98 assay with S9 activation.	Ndhala et al., 2010; 2011.

Liver toxicity associated with herbal medicines

Traditional herbal medicines associated with human liver injury.

Plant species	Constituent	Clinical/Experimental observations	References
<i>Larrea tridentata</i> (DC.) Coville (chaparral)	nordihydro-guaiarectic acid (?)	Leaves from a desert shrub which are traditionally used in Southwestern USA and Mexico for a variety of therapeutic indications. Reports of hepatocellular injury and cholestatic hepatitis (jaundice, marked increase of ALT) after weeks of use symptoms generally resolved on ingestion cessation.	Sheikh et al., 1997.
<i>Teucrium chamaedrys</i> L., <i>T. polium</i> L., <i>T. viscidum</i> Blume, <i>T. capitatum</i> L., (germander)	furano-diterpenoids	Europe and Middle East, blossoms traditionally used to treat various conditions. Reports of hyperbilirubinemia, anorexia, nausea, marked elevations of ALT, after 2 months of use. Some cases, fulminant hepatitis requiring liver transplantation.	Larrey et al., 1992; Lekehal et al., 1996; Mimidis et al., 2009.
<i>Piper methysticum</i> G. Forst. (kava kava)	piper-methysticin (?)	South Pacific traditional use as a recreational and ceremonial drink. Reports of hepatocellular and cholestasis pattern of liver injury, highly variable cumulative doses and latency periods. some underwent liver transplantation. Idiosyncratic DILI.	Moulds and Malani, 2003; Olsen et al., 2011; Teschke, 2010.
<i>Symphytum officinale</i> L. (comfrey) <i>Senecio</i> sp., <i>Heliotropium</i> sp., <i>Crotalaria</i> sp.	pyrrolizidine alkaloids	Europe, Asia, South Africa, USA, Jamaica, worldwide traditional medicine. venous occlusive disease, abdominal pain, ascites, slight jaundice and hepatomegaly (similar to Budd-Chiari Syndrome).	Steenkamp et al., 2000; Zuckerman et al., 2002.
<i>Atractylis gummifera</i> L.	atractylosides, gummiferin	Mediterranean region use as antipyretic, emetic, diuretic, chewing gum. Acute hepatitis, nephrotoxicity, hepatorenal failure.	Daniele et al., 2005; Larrey, 1997.
<i>Callilepis laureola</i> DC.(Impila)	atractylosides	South Africa use in Zulu traditional medicine. Acute liver and kidney injury, abdominal pain, diarrhea, vomiting, high mortality.	Popat et al., 2001; 2002.
<i>Chelidonium majus</i> L.	celandine	Europe and temperate regions of Asia. Used to treat dyspepsia, biliary colic, cholelithiasis. Several case reports describing acute liver injury, moderate elevations of ALT, marked cholestasis, recovery after herbal medicine discontinuation.	Benninger et al., 1999; Seeff, 2007.
Mixture of plants (Herbalife® products)	(?)	Widespread use as food supplement. Case series of fulminant liver failure, hepatocellular damage, veno-occlusive disease and cholestasis.+	Bunchorntavakul and Reddy 2013; Manso et al., 2011; Schoepfer et al., 2007; Teschke et al., 2012.

+The comment of Herbalife® manufacturers on the report of DILI cases possibly associated to their product is found in a letter by Appelhans et al. (2013) and authors' reply in Reddy and Bunchorntavakul (2013).

Conclusion

The safe use of medicines requires both a pre-clinical and clinical evaluation of toxicity and post-marketing Pharmacovigilance

Post-marketing pharmacovigilance is essential to bring problems of effectiveness and rare adverse effects, the occurrence of which is not anticipated by experimental and clinical studies

In order to ensure the quality and safety of herbal medicines,

WHO should propose global unified planning, which includes global management standards and quality standards,

Radical source of herbs, seed and seedling breeding, planting, harvesting and storage, rational proceeding, manufacture, and quality standards

In contrast to newly developed conventional drugs, the safety assessment of traditionally used herbal medicines can also take into account a pre-marketing spontaneous report of ADR

Finally, it should be emphasized that even though traditional use does not ensure the safety and effectiveness of herbal medicines

It is a useful guide for identification of new pharmacologically active substances in plants

A reverse pharmacology/toxicology or “bedside-to-bench” approach starting with a rigorous collection of clinical data in field surveys, as suggested by Graz (2013), may also be a fruitful strategy to improve knowledge on the safety of traditionally used herbal medicines

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Thank You



