

Regulation and application of Chinese herbs in the US: misuse is the main cause of toxic incidents

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The World Health Assembly endorsed the revised International Classification of Diseases (ICD) at its 72nd meeting in 2019 and the revisions came into effect globally on January 1, 2022. The World Health Organization (WHO) included a chapter for the first time in the 11th Revision of the ICD that discussed traditional Chinese medicines (TCM)^[1]. Including TCM in ICD-11 recognizes TCM for its past contribution to world healthcare and acknowledges the current need for TCM in the world health framework.

Despite this advance, the European Academies Science Advisory Committee (EASAC) and the Federation of European Academies of Medicine (FEAM) issued a joint statement regarding safety and efficacy concerns of TCM usage. One of these concerns was that “patients may be encouraged to self-administer unregulated products or seek unregulated diagnostic procedures outside of the remit and responsibility of public health services”^[2]. This concern is reasonable because Chinese herbal medicines (CHMs) are regulated as dietary supplements in most Western countries^[3]; therefore, an incorrect self-diagnosis or misuse of Chinese herbs by consumers can cause safety issues.

CHM has been used in China for more than 2000 years. Chinese immigrants introduced CHM to American and Europe and the use of CHM increased in these regions^[4]. Although CHM has successfully brought relief from various illnesses, including coronavirus disease 2019 (COVID-19), and has saved many lives in Western countries^[4–7], negative reports have tainted the reputation of these treatments. The two most reported incidences are those of ephedra-linked deaths of people who took ephedra products for weight loss and energy^[8,9] and the outbreak of renal failure among women who took a product containing aristolochic acid (AA) as a weight-loss regimen^[10]. These reports have undermined the safety of CHM, which has become a major concern for health professionals of conventional medicine and consumers in the US and other Western countries. CHM was unjustly considered the reason for health problems by some patients^[11]. The

ephedra-linked deaths and AA renal failure cases were caused by the misuse of CHM because the Chinese herbs used as dietary supplements by consumers without prescriptions by TCM practitioners should not be included in the category of CHM.

The efficacy and toxicity of CHM have been documented by generations of TCM doctors since ancient times. Factors that affect the safe application of CHM, including methods to reduce toxicity, such as the processing of materials^[12,13] and compatibilities^[14,15], have been summarized and recorded.

With the development of modern examination techniques and network information exchange, safety evaluations have evolved in their specificity and accuracy. Scientists have found that liver toxicity resulting from the use of certain herbs occurs only in a few people with specific genes.

This study briefly reviewed the history of CHM in the US and provided an introduction to CHMs and their toxicities, a discussion of factors that impact the safe and effective application of these treatments, animal studies for safety evaluation, and suggestions for research and safe application of CHM.

Definition of TCM, Chinese material medica (CMM), CHM, and factors that impact the safe application of Chinese herbs

The public is generally unaware of the differences among TCM, CMM, CHM, and Chinese herbs.

TCM refers to a comprehensive medical system involving CMM, acupuncture, or other therapeutic methods to prevent and treat diseases under the guidance of TCM theories based on TCM diagnosis and differentiation. It is an empirical science that studies the laws of health and disease transformations in human life activities, as well as disease prevention, diagnosis, treatment, rehabilitation, and healthcare.

CMM are the most common therapeutic methods in TCM and they involve the use of natural medicines by

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TCM doctors to treat diseases under the guidance of TCM theories based on formulas. Although TCM is a medical system, TCM and Chinese medicine (CM) are used as synonyms for CMM or CHM in many articles.

CMM consists of plant, animal, and mineral materials. Plant-sourced CMM are called CHM and account for approximately 87% of all CMM. Therefore, CHM is the main form discussed in this article. CMM and CHM are termed CMs when they are prescribed in the form of TCM formulas to treat diseases. CMM are regulated as dietary supplements and not medicines in the US and the related medicines are generally referred to as Chinese herbs in that country.

TCM practitioners have discovered that the formulation of herbs and processing of herbal materials can enhance therapeutic efficacy and reduce toxicity. The compatibility among the various herbs and processing methods is well documented^[12-15].

The categorization of Chinese herbs as dietary supplements in the US induces the public to believe that these products are safe because they have natural sources, when in fact they are only safe when used properly. Therefore, some consumers self-diagnose and self-prescribe based on information from the internet or friends rather than obtaining a prescription from a TCM practitioner. Such uses can readily lead to adverse effects and toxicity.

CHM side effects or toxicities can also occur when inexperienced TCM practitioners provide incorrect diagnoses; however, these incidences are much lower than those reported by consumer self-prescription.

The following factors can affect the efficacy and safety of Chinese herbs: quality of the materials and processing; diagnosis and syndrome differentiation; dosage and duration of administration; formulation; and herb-drug interactions.

A modern TCM practitioner with knowledge of the pharmacology of Chinese herbs and the pathology and pharmacology of conventional medicine can help in the safe application and prescription of CHM.

Chinese herbs in the US

CHM was brought to the US by Chinese immigrants during the gold rush era^[4]. TCM practitioners have helped countless patients with various diseases using CHMs. However, owing to the lack of proper regulations, toxic incidents inevitably occurred.

Successful CHM treatments

A holistic view of the human body and its diseases is the main feature of TCM. This practice believes that symptoms that physicians cannot diagnose or diseases with no available treatment in conventional medicine are caused by the imbalance of yin and yang, or qi and blood, which are related to regulatory dysfunction of the immune, nervous, or hormone systems. Experienced TCM practitioners can often provide considerable relief to patients with such symptoms or diseases using CHM, as shown in the following examples:

Ing “Doc” Hay was an early TCM practitioner who arrived in the US in the 1800s. He was respected as a

city treasure in John Day, Oregon because he “could cure diseases others couldn’t; ... all his patients survived the fatal Spanish Flu epidemic in 1919... When the conventional doctors tried to have Hay prosecuted for practicing medicine without a license, no jury would convict him. For them, his record was license enough”^[5].

In 1862, Jane Stanford, the wife of Governor Leland Stanford, suffered a lethal pulmonary condition. Her Western physicians declared no further hope; therefore, under the recommendation of his Chinese servant, Governor Stanford urgently summoned the herbal doctor Yee Fung Cheung. Yee saved Mrs. Stanford’s life with a herbal mixture containing Ephedrae Herba (Ma Huang)^[6,7], which is a common Chinese herb that is still used for treating pulmonary illnesses in China but is currently banned in the US.

With the growing number of TCM practitioners in the US, such miracle stories are now heard frequently. However, the many successful CHM treatments are rarely reported, whereas negative outcomes regarding Chinese herbs are widely published by the media.

Toxic incidents caused by the misuse of Chinese herbs

Ephedrae Herba is a commonly used herbal medicine in China that is not used for energy or weight loss in TCM. Ephedrae Herba was not well known in the US until over a hundred ephedra-linked deaths were reported^[8,9]. On February 9, 2004, the Food and Drug Administration (FDA) issued a final rule prohibiting the sale of dietary supplements containing ephedrine alkaloids (ephedra) because such supplements presented an unreasonable risk of illness or injury^[16].

Similarly, a product in Belgium was related to kidney failure of a group of women who were taking it for weight loss. In this case, AA was identified as the toxic compound in an adulterated herb of *Stephaniae Tetrandrae Radix* (Fang Ji)^[17]. As a result, CHMs or their adulterates containing AA, such as *Aristolochiae Fructus* (Ma Dou Ling), *Aristolochiae Herba* (Tian Xian Teng), *Radix Aristolochiae* (Qing Mu Xiang), *Radix Aristolochiae Fangchi* (Guang Fang Ji), *Caulis Aristolochiae Manshuriensis* (Guan Mu Tong), and *Asari Radix et Rhizoma* (Xi Xin) were banned in the US and Europe. Consequently, AA nephropathy was named after this incident.

The general public is unaware that both of these incidents were caused by CHM misuse. There are no records of Ephedrae Herba or *Stephaniae Tetrandrae Radix* being used as stimulants or weight loss inducers in TCM. These two products were manufactured by Western businesses and sold as dietary supplements. They were not prescribed by TCM practitioners.

Toxic incidents involving Chinese herbs caused by the ignorance of sellers or consumers

There is no requirement for professional training or certification for sellers of Chinese herbs in the US. Many sellers are unaware of the identity or safe dosages of Chinese herbs and this ignorance by both the seller and consumer can lead to negative outcomes.

On March 10, 2017, the officer of the San Francisco Department of Public Health issued a report titled “Herbal Tea Poisons Two San Franciscans - Public Warned to Discard Tea Purchased at Chinatown Shop,” with the explanation that “A plant-based toxin, aconite, was found in lab tests of the patients and the tea samples they provided”^[18]. These incidents occurred because the owner of the Chinatown shop did not know the materials in the herbal tea he was selling.

Sellers of Chinese herbs should be aware of the quality and safe dosages of each product in their inventory. In addition, these merchants should receive professional training that involves a TCM pharmacist certificate or diploma.

Consumers must understand that Chinese herbs are medicines and not dietary supplements and that they are safe only when used under certain conditions. TCM emphasizes syndrome differentiation based on diagnosis. The self-use of Chinese herbal formulas or products based on information from the internet or recommendations from friends increases the risk of negative effects.

Regulation of Chinese herbs in the US

Traditionally, CHM should be prescribed by TCM practitioners under the guidance of TCM theory and based on clinical diagnosis and differentiation.

The US FDA regulates Chinese herbs as dietary supplements under the Dietary Supplement Health & Education Act of 1994 (DSHEA)^[19]. Dietary supplements are regulated as food and not as drugs; therefore, no prescription is required for their purchase. In addition, the FDA has established labeling rules that disallow claims of disease prevention and treatment on the labels of dietary supplements. This further misleads consumers in terms of the proper use of Chinese herbal products as the health conditions covered and dosage terms are not considered. Long-term usage of these products may cause side effects. The Ephedrae Herba and AA incidents are examples of CHM misuse.

The current good manufacturing practice (cGMP) for dietary supplements in the US was implemented in 2007^[20]. Since then, Chinese herbs imported or manufactured in the US have been subject to the GMP regulations. Herbs and herbal products are now tested for pesticides, heavy metals, and microbial contamination; however, GMP regulations are not sufficiently strict. Unlike food processing plants, FDA officers do not often inspect the locations of dietary supplement manufacturers. Instead, GMP are determined based on the conscious implementation of manufacturers and product owners. Reputable manufacturers prove their compliance using third-party GMP certification. Many smaller manufacturers do not have testing laboratories and send their samples to contractors for testing.

In addition to ephedra and AA-containing herbs, the FDA has banned other CMMs, including Hominis placenta (Zi He Che), Faeces Troglodyterori (Wu Ling Zhi), Arecae pericarpium), (Da Fu Pi), Arecae semen (Bin Lang), and Bombyx Batryticatus (Bai Jiang Can)^[3].

Certain CMMs are regulated (require an export permit) and/or prohibited (no import allowed) by the

Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES). Sturgeon summarized the restricted list of Chinese herbs and resources in 2011^[3].

Research and education regarding Chinese herbs in the US

United States scientists became interested in Chinese herbs after the American Herbal Pharmacology Delegation visited China in 1974 to study the basic and clinical pharmacology of traditional CMM. The delegation comprised 12 specialists in chemistry, medicine, pharmacology, pharmacognosy, pharmacy, and Chinese culture. Subsequent to this visit, the National Academy of Sciences published “Herbal Pharmacology in the People’s Republic of China”^[21].

The Office of Dietary Supplements (ODS) was established in 1995 by the National Institutes of Health (NIH) to promote scientific research in the area of dietary supplements, including plant extracts. TCM is considered part of complementary and integrative medicine in the US and the NIH created the National Center for Complementary and Integrative Health (NCCIH) to conduct and support TCM research.

However, because American scientists at universities and researchers at pharmaceutical companies are not familiar with TCM and CHM clinical applications, the studies focused mainly on screening biologically active compounds from CHMs. These studies failed to provide the expected results because the designs were not based on the TCM clinical application of the herbs^[22,23].

Yung-Chi Cheng, a pharmacology professor at Yale University, successfully developed a botanical drug for liver cancer, YIV-906 (PHY906), based on the traditional CHM formula Huang Qin tang (*Scutellaria* decoction) first recorded 2000 years ago. PHY906 plus capecitabine is currently undergoing clinical trials as a hepatocellular carcinoma treatment^[24].

Colleges and universities in the US that teach Chinese and oriental medicine offer courses in CHMs and formulas. Although the examination for an acupuncture license includes CHMs and formulations in California and certain other states, and the National Certification Commission for Acupuncture and Oriental Medicine (NCCAOM) issues a diploma in Chinese herbology and oriental medicine, no professional license is required to prescribe Chinese herbs. These herbs and related products can be easily obtained from shops or on-line. The increase in the availability of Chinese herbs from on-line suppliers heightens the risk of misuse and negative effects for consumers who have no basic knowledge of CHM.

Quality control of Chinese herbs

Dietary supplements are regulated by the FDA; however, the FDA generally does not review dietary supplements before they are sold to consumers and is mainly involved after the products enter the market. The FDA only requires that the facility be registered; no registration or approval for dietary supplements is required by the FDA unless they contain new ingredients or plant varieties that are not listed by the FDA^[25].

Manufacturers and owners of Chinese herbs are expected to ensure the quality of their materials and products.

The American Herbal Pharmacopoeia (AHP) began to develop qualitative and therapeutic monographs in 1994 and expects to produce 300 botanical monographs, including many of the Ayurvedic, Chinese, and Western herbs most frequently used in the United States^[26]. The Dietary Supplements Compendium (DSC) issued by The US Pharmacopoeia (USP) is updated periodically^[27] and contains information for dietary supplement manufacturers and ingredient suppliers. This manual provides step-by-step procedures and assays for the quantitative and qualitative testing of raw materials and finished dietary supplement products.

For herbal products, the ingredients and finished products must be identified and tested for pesticides, microorganisms, and heavy metals.

False testing for ingredients and finished products can occur in testing laboratories, including those of third-party-certified contractors. Some business owners of dietary supplement ingredients or products have no basic knowledge of the items they sell or produce and adulterated or contaminated Chinese herbal products can circulate owing to the lax regulations. Consumers should be cautious when choosing Chinese herbal products and consult CHM experts when possible.

Liver toxicity of Chinese herbs

According to LiverTox, an on-line resource for information on drug-induced liver injuries from prescription and over-the-counter drugs, herbal products and dietary supplements provided by The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) under NIH in collaboration with the National Library of Medicine (NLM), specific Chinese and other Asian herbal medications implicated in liver injury include *Dysosma pleianthum* (Ba Jiao Lian), *Fructus psoraleae* (Bol Gol Zhee), *Breynia officinalis* (Chi R Yun), *Lycopodium serratum* (Jin Bu Huan), *Ephedra sinica* (Ma Huang), *Xiao Chai Hu tang*, and *Shou Wu pian*^[28].

Polygoni Multiflori Radix (He Shou Wu) is a common tonifying and anti-aging herb that is widely used to treat gray hair and hair loss. The liver toxicity of this herb was unclear until recently, when the database became available, at which time the toxicity of this compound has attracted considerable attention. A research team in China found that the liver injury caused by *Polygoni Multiflori Radix* and a few other herbs may be related to individual health conditions and genetics (specific genes), known as idiosyncratic toxicity^[29]. That study revealed the immune idiosyncratic properties of liver injury and discovered the related susceptibility gene, HLA-B* 35:01^[30]. This was the first study to report a susceptibility gene for liver damage from Chinese herbs.

The term idiosyncratic toxicity means that the herb itself has no obvious direct toxicity and the toxic effects are mainly related to the immunity, metabolism, physical constitution, and other genetic factors of the patient. These compounds only cause injury to a small number of susceptible individuals^[29].

The characteristics of idiosyncratic toxicity are as follows: there is no clear dose-dependent relationship, the toxicity is difficult to predict, and the toxicity is difficult to replicate in normal animal models.

Categorization of CMM according to safety

Chinese herbs are regulated for use as dietary supplements in the US and these regulations could be interpreted by the American public as acknowledgment of the safety and non-toxicity of Chinese herbs. Therefore, misuse and abuse are the greatest impediments to the safe use of CM.

CMM toxicity has been recorded since ancient times

The safety and efficacy of CHM depend on dosage and time of administration as well as syndrome differentiation. *Shen Nong Ben Cao Jing* (*Shennong's Materia Medica*) was the first book that discussed CMM, written 2000 years ago. It classified 365 plant, animal, and mineral species into three categories, based on their efficacy and toxicity^[31]. The entry for each medicinal substance included the nomenclature, properties, compatibilities, and medical applications.

Materials in the high-grade (superior) category included tonic substances mainly used for maintaining health and restoring body balance with no or few unfavorable side effects. Medium-grade (mediocre) compounds comprised herbs with mild side effects if administered improperly, particularly when prolonged or overdosed. The low-grade (inferior) substances were toxic and to be used only at the suggested doses for the treatment of specific diseases. "Stop taking soon after the formula take effect." Administration of longer or higher doses could cause safety issues.

Toxic herbs recorded in Chinese Pharmacopoeia

The most toxic CMM have been well documented and studied. The 2020 Pharmacopoeia of the People's Republic of China recorded 84 toxic CMM, including 10 containing major poisons, 43 deemed poisonous, and 31 containing minor poisons^[32]. In addition, this resource lists 95 CMM that are toxic to the reproductive system, including 37 that should be banned and 58 that should be used with caution.

Over the long history of fighting disease, TCM practitioners have discovered the therapeutic effects of herbs, learned processing techniques to reduce the side effects or toxicity of CHM, and determined that proper combinations of herbs can enhance the efficacy or reduce the toxicity of the compound, while improper combinations can cause side effects or greater toxicities. Therefore, the pairs of compatible and incompatible CMM were summarized as the "eighteen antagonisms and nineteen mutual inhibitors" (Tables 1 and 2).

Why are toxic herbs used in TCM?

Toxic CMM play an important role in complex diseases including cancers^[33] because they can combat the poison in the body under special conditions. TCM theory states that "the disease takes it when disease is present, and the body takes it when no disease." In

Table 1
Eighteen antagonisms

Names (English, <i>Latin</i>)	Antagonist
Wu Tou (aconite root, <i>Aconiti Radix</i>)	Ban Xia (pinellia, <i>Pinelliae Rhizoma</i>)
	Gua Lou (Mongolian snakegourd fruit, <i>Trichosanthis Fructus</i>)
	Bei Mu (thunberg fritillary bulb, <i>Fritillariae Thunbergii Bulbus</i>)
	Bai Lian (Japanese ampelopsis root, <i>Ampelopsis Radix</i>)
	Bai Ji (Common bletilla tuber, <i>Bletillae Rhizoma</i>)
Gan Cao (licorice root, <i>Glycyrrhizae Radix et Rhizoma</i>)	Hai Zao (seaweed, <i>Sargassum</i>)
	Da Ji (Euphorbia, <i>Euphorbiae Pekinensis Radix</i>)
	Gan Sui (kansui root, <i>Kansui Radix</i>)
	Yuan Hua (lilac daphne flower bud, <i>Genkwa Flos</i>)
Li Lu (hellebore, <i>Veratri Radix et Rhizoma</i>)	Ren Shen (ginseng, <i>Ginseng Radix et Rhizoma</i>)
	Sha Shen (upright ladybell root, <i>Adenophorae Radix</i>)
	Xuan Shen (figwort root, <i>Scrophulariae Radix</i>)
	Dan Shen (salvia, <i>Salviae Miltiorrhizae Radix et Rhizoma</i>)
	Ku Shen (sophora root, <i>Sophorae Flavescens Radix</i>)
	Xi Xin (asarum, <i>Asari Radix et Rhizoma</i>)
	Shao Yao (paeonia root, <i>Paeoniae Radix</i>)

this sense, “it” refers to “toxicity”. In addition, “No death if used for a reason,” means that if a patient has a disease, the herbs will target the disease and not harm the body.

For example, arsenic has been used in conjunction with other CMM to treat cancer. An arsenic trioxide injection was developed to treat acute promyelocytic leukemia (APL)^[34], a cancer of the blood cells. Similarly, processed aconite (*Radix Aconiti Lateralis Preparata*, Fu Zi) is a Chinese herb commonly used for heart failure^[35], while Thunder God Vine (*Radix Tripterygii Wilfordii*, Lei Gong Teng) is effective in treating rheumatoid arthritis and cancer^[36,37]. Formulations are prepared with these CMM to mitigate the toxicity of the individual herbs.

Why do toxic incidents happen?

Skilled TCM practitioners know how to safely use toxic herbs to treat diseases successfully; however, side effects can occur when inexperienced TCM practitioners and uninformed consumers use toxic or non-toxic herbs improperly without syndrome differentiation.

Table 2
Nineteen mutual inhibitors

Names (English, <i>Latin</i>)	Mutual inhibitor
Liu Huang (sulfur, <i>Sulfur</i>)	Bu Xiao (mirabilite glauher's salt, <i>Natrii Sulfas</i>)
Shui Yin (mercury, <i>Hydrargyrum</i>)	Pi Shuang (arsenic, <i>Arsenicum</i>)
Lang Du (wolfsbane, <i>Euphorbiae Ebracteolatae Radix</i>)	Mi Tuo Seng (litharge, <i>Lithargyrum</i>)
Ba Dou (croton, <i>Crotonis Fructus</i>)	Qian Niu (lobedleaf pharbitis seed, <i>Pharbitidis Semen</i>)
Ding Xiang (clove, <i>Caryophylli Flos</i>)	Yu Jin (aromatic turmeric root-tuber, <i>Curcumae Radix</i>)
Chuan Wu (Sichuan aconite main root, <i>Aconiti Radix</i>)	Xi Jiao (rhinoceros horn, <i>Rhinoceri Cornu</i>)
Cao Wu (kusnezoff monkshood root, <i>Aconiti Kusnezoffii Radix</i>)	
Ya Xiao (mirabilite glauher's salt, <i>Natrii Sulfas</i>)	San Leng (common burreed rhizome, <i>Sparganii Rhizoma</i>)
Gong Gui (cassia bark, <i>Cinnamomi Cortex</i>)	Shi Zhi (holloysite, <i>Halloysitum Rubrum</i>)
Ren Shen (ginseng, <i>Ginseng Radix et Rhizoma</i>)	Wu Wei Zi (peteropus, <i>Trogopterori Faeces</i>)

Chinese herb-induced poisoning or side effects can occur with the use of adulterated or alternative materials, material contamination from microorganisms or heavy metals, and improperly processed materials, as well as through overdose, extended use, inappropriate diagnosis and differentiation, or inappropriate formulations^[33].

The author of *Shennong's Materia Medica* stated that a formula should use herbs that provide mutual reinforcement or assistance and not those that produce mutual antagonism or inhibition. If a toxic herb is present in a formula, other materials that have the effect of mutual suppression or restraint can be used to reduce toxicity.

Practitioners who prescribe CHM formulas must know the safe dosage of each herb in the formula and whether the formula is suitable for the particular condition. TCM theory states that the balance of *yin-yang* and the harmony of *qi* and blood are crucial for health. Once the balance of *yin and yang* and the harmony of *qi* and blood in the human body are disrupted, *qi* and blood become disordered; consequently, the organs become dysfunctional, and the body becomes ill or dies. For example, excessive water consumption can disrupt the state of the body and cause death. CMM restore this balance.

Toxicities of Chinese herbs have been mistakenly reported

Chinese herbs have been misrepresented, both intentionally and unintentionally, in the past years. Two examples are presented.

A report of AA-containing products causing kidney failure resulted in a TCM practitioner in Belgium being sued by a patient for the administration of AA-containing herbs. The practitioner was sentenced in 2015, despite the insistence that the herbs prescribed to this patient did not contain AA. The practitioner was exonerated with professional support from TCM experts from the US and China^[11].

In August 2023, the article “Maternal Traditional Chinese Medicine Exposure and the Risk of Congenital Malformations”^[38] published in the journal *Acta Obstetrica et Gynecologica Scandinavica* (AOGS paper) was retracted because queries were raised by TCM and CHM experts in the US^[35]. “The retraction related to flaws with the study design in collecting data on exposure to TCM by pregnant people, which affected the validity of the data to support the conclusions of the study”^[38].

The tampering of the conclusions of several cited references in the AOGS paper suggests that the author was intentionally attempting to damage the reputation of CHM. Similarly, the acceptance of an article with such obvious mistakes in publication revealed reviewer bias against CHM.

The media only reported the details of the first sentence in the Belgian case and the publication of the AOGS paper. The final exoneration and the retraction of the AOGS paper were not widely covered.

Safety evaluations of Chinese herbs through animal testing

The formulation of a sulfa antibiotic dissolved in ethylene glycol resulted in the death of 107 people; therefore, animal testing was mandated for new drug development in the US in 1938^[39]. Animal testing has since been used to study the safety of CHMs and to develop new drugs in China.

Animal studies are required for novel drugs prior to their use with humans. However, these rules do not apply to CHMs, since it is somewhat redundant for a herb or formula that has been used for hundreds or thousands of years to require an animal study to evaluate its safety.

To evaluate the safety of animal studies, the following must be considered: healthy and diseased individuals exhibit different characteristics. A healthy person is in a normal physiological condition, whereas a diseased person is in a pathological condition. Studies on healthy animals may lead to incorrect conclusions regarding safety.

For example, 20 Chinese herbs that are commonly used to treat ill pregnant people were administered to healthy pregnant mice at clinically relevant doses. That study concluded that “reproductive toxicity of commonly used CHM during pregnancy was confirmed in mice”^[40]. These results, with 10 mice per group, cannot verify whether the tested herbs have reproductive toxicity in pregnant humans.

Disease-syndrome-based toxicology is either based on clinical real-world cases or uses animal models that mimic the conditions of diseases and syndromes to study the different responses to the toxic effects of CHM

between the normal and sick states of the body and to investigate CHM safety more realistically and comprehensively^[29]. Some herbs are only toxic to a particular group of people with specific genes and are not toxic to healthy animals.

Two examples of these herbs are *Polygoni Multiflori Radix* and *Rhizoma Coptidis*. The liver toxicity of *Polygoni Multiflori Radix* is discussed in “Liver toxicity of Chinese herbs” section. *Rhizoma Coptidis* contains the alkaloid berberine, which can increase bilirubin formation and elevate the risk of jaundice, especially in infants with glucose-6-phosphate dehydrogenase (G6PD) deficiency^[41]. The toxicities of some Chinese herbs vary depending on animal species.

Studies have shown that the reproductive toxicity of Chinese herbs varies among species. For example, researchers found that realgar had obvious reproductive toxicity in pregnant rabbits, whereas rats were relatively insensitive to this substance^[42]. The safety of compounds isolated from a herb differs from that of its water decoction.

Changes in chemical composition alter biological activity and toxicity and compounds isolated and purified from Chinese herbs have different chemical and biological activities; therefore, these compounds are not identical to the traditional herbal decoctions.

Scientists have raised concerns regarding the concordance between animal and human trials. Dr. Van Norman, the author of “Limitations of animal study for predicting toxicity in clinical trial, is it time to rethink our current approach?” stated that the Helsinki Declaration requirement that human experiments be “designed and based on the results of animal experimentation” was not scientifically derived; therefore, such a requirement would not necessarily improve the safety or efficacy of a particular drug in humans. Van Norman cited several reviews of animal and human toxicity studies, including one analysis of 2,366 drugs, and concluded that “results from tests on animals (specifically rat, mouse, and rabbit models) are highly inconsistent predictors of toxic responses in humans.” In addition, he stated that “Although animal toxicity testing has been the stalwart basis of ‘ensuring’ safety of in-human clinical testing and use, examination of the published data raises significant questions about whether it is reliable and should be abandoned or at least significantly curtailed in favor of other potentially more reliable methods”^[39].

Suggestions

The importation of Chinese herbs, herbal extracts, and herbal products into the US is increasing, which indicates that an increasing number of people are accepting TCM and CHM. Therefore, the safe application of Chinese herbs has become increasingly relevant.

Traditionally, CHM has been used under the guidance of TCM theories and was prescribed by practitioners based on TCM diagnosis and differentiation. However, as Chinese herbs are regulated as dietary supplements in the US, consumers lack an understanding of TCM and CHM, and the safety of Chinese herbs has become a concern for physicians and consumers.

The following items are suggested to ensure the effective and safe application of Chinese herbs: education. The FDA, NIH, other organizations, and experts in CHM should provide on-line education to American consumers. Consumers should consult CHM experts prior to receiving CHM treatment. Business owners involved in the sale of Chinese herbs should be knowledgeable of CHM. The FDA should strengthen its supervision of toxic Chinese herbs. The FDA should have a commission of experts that consult on the use of Chinese herbs.

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