# AACT Herbal Dietary Supplement Section Abstracts

January 2025

1. **Mitragyna speciosa Korth toxicity: Experimental findings and future prospects**. J Taibah Univ Med Sci. 2024 Dec 12;19(6):1143-1156. doi: 10.1016/j.jtumed.2024.12.002. eCollection 2024 Dec.

   Begum T, Arzmi MH, Helal Uddin ABM, Khatib A, Abbas SA, Ahmed QU

   Mitragyna speciosa (Roxb.) Korth, locally known as kratom, is a traditional medicinal plant from Southeast Asia, with mitragynine as its principal alkaloid. Similar to other medicinal plants, kratom has side effects and toxicities, which have been documented in scientific studies and case reports. The mitragynine sale and possession of kratom are prohibited in Malaysia but legalized in Thailand. In the US, kratom is not lawfully marketed as a drug product, a dietary supplement, or a food additive in conventional food. Despite these restrictions, individuals continue to self-administer kratom to alleviate various health problems, often without a comprehensive understanding of the associated toxicities. Hence, the primary aim of this review is to provide a comprehensive overview of the toxicities associated with kratom, drawing from scientific studies, case reports, and other relevant sources. It also addresses the management of these toxicities, identifies gaps in existing studies, and discusses future perspectives. Therefore, a literature review search was conducted to gather essential information for this review. The in vitro studies focused on metabolizing enzymes, indirectly indicating kratom toxicity. By contrast, the in vivo results directly demonstrated kratom's toxic effects on the liver, kidneys, lungs, and brain. Case studies, primarily from Western countries, involved both single and combination use of kratom. Thus, by shedding light on these aspects, we aim to enhance awareness among healthcare professionals and the general public. Additionally, identifying existing gaps can guide future scientific studies. Since prevention is better than cure, this review holistically presents information about the toxicities associated with the use of kratom leaves, serving anyone seeking to understand and prevent kratom-related toxicities.

   DOI: 10.1016/j.jtumed.2024.12.002
   PMCID: PMC11720435
   PMID: 39802218

2. **Effects of Taking Herbal Medicines in Early Gestation on Pregnancy and Placental Formation** Yakugaku Zasshi. 2025;145(1):53-60. doi: 10.1248/yakushi.24-00174-3.

   Sakurai T.

   The use of Japanese herbal medicines (Kampo medicines), rooted in centuries of raditional practice, lacks extensive Western scientific validation regarding their safety. Concerns include potential risks such as placental dysplasia, miscarriage, teratogenicity, and fetotoxicity when administered to pregnant women. Therefore, scientific safety evaluations are crucial for the appropriate use of Kampo medicines during pregnancy. Critical physiological processes such as implantation, invasion into the endometrium, placentation, and fetal development are vital for establishing a successful pregnancy. The placenta, forming from implantation until birth, is

essential for fetal growth and nutrition. Proper placental function relies on the regulated differentiation and development of specific trophoblast cell lineages. If Kampo medicines impact these cell lineages, there may be increased risks of fetal developmental issues and pregnancy complications. current studies often neglect evaluating placental function or formation, focusing primarily on fetal toxicity and teratogenicity. Thus, assays for placental function and placentation toxicity are needed. This review consolidates existing knowledge on the effects of Kampo medicines, herbs and herbal medicines on pregnancy and placentation, emphasizing the necessity for scientific safety assessments to guide their use during pregnancy. Ensuring accurate information and safety of Kampo medicines, herbs and herbal medicines for pregnant women is essential to safeguard the health of the mother, fetus, and placenta.

DOI: 10.1248/yakushi.24-00174-3
PMID: 39756926 [Indexed for MEDLINE]

3. **Safety of herbal medicines used in early gestations among the Chinese population: A population-based cohort study.** Phytomedicine. 2024 Dec;135:156197. doi: 10.1016/j.phymed.2024.156197. Epub 2024 Oct 28.

Tan J, Xiong Y, Zhao P, Liu C, Ren Y, Chen M, Yao G, Qian Y, Rong B, Qi H, Chen M, Sun X.

BACKGROUND: Herbal medicines have a long history of use for pregnant women around the world. However, their use in the early pregnancy is often questioned in terms of safety on offspring.
PURPOSE: To investigate whether herbal medicines used at early pregnancy are associated with an increased risk of birth defects.
STUDY DESIGN: The population-based retrospective cohort study included pregnancies registered in a population-based and long-term follow-up database (i.e., REPRESENT) with live births between January 2013 and December 2018, by linking a population-based drug prescription database covering all the hospitals in Xiamen, China.METHODS: The exposure of interest was defined as the consecutive administration of one or more prescriptions of herbal medicines to prevent miscarriage during the first trimester. We examined the overall birth defects (excluding chromosomal malformations) and 23 individual types by national surveillance. To facilitate comparison, we included blank (non-use) and active controls. Poisson regression based on propensity score matching (PSM) was applied to control for the confounders. Multiple sensitivity analyses and negative control analyses were conducted to examine the robustness.
RESULTS: The final cohort included 195,824 pregnancies, and 29,063 (14.8 %) were prescribed with herbal medicines at early pregnancy, of which 3,024 (1.5 %) received herbal medicine monotherapy. These herbal medicines were often used in combination with other medicines (especially pharmaceutical medicines) and peaked between the fifth and eighth gestational weeks. A total of 2,795 birth defects were identified. Compared to progesterone monotherapy (i.e., active control), herbal medicine monotherapy was not associated with a higher risk of overall birth defects (relative risk [RR] 1.28, 95 %CI 0.57-2.90). Compared to no use of drug (i.e., blank control), pregnancies with herbal medicine monotherapy showed a similar risk (RR 1.25, 95 %CI 0.69-2.29). Consistent results were shown in sensitivity analyses.

CONCLUSION: The current evidence dose not suggest an increased risk of birth defects when using herbal medicines in early pregnancy, although larger studies with wider pregnancy populations are needed for further confirmation.

DOI: 10.1016/j.phymed.2024.156197
PMID: 39515097 [Indexed for MEDLINE]

4. **Herbal abortion: Non-toxic method, dangerous representation**. Am J Emerg Med. 2025 Jan;87:184-185. doi: 10.1016/j.ajem.2024.09.012. Epub 2024 Sep 10.

   Dutton-Kenny M, Horner D.

DOI: 10.1016/j.ajem.2024.09.012
PMID: 39271399

5. **Kampo medicine inducing drug-induced liver injury: A case report and systematic review.** Drug Discov Ther. 2025 Jan 14;18(6):325-335. doi: 10.5582/ddt.2024.01087. Epub 2024 Dec 29.

   Hoshi A, Funakoshi H, Otoyama Y, Yoshida H, Momo K.

   Kampo medicine, comprising various conventional crude drug products, poses challenges in identifying adverse event causality. We present a case of severe liver injury following the administration of Saibokuto and attempted to identify the likely causative crude drug inducing liver injury through a systematic literature review. A 29-year-old woman developed severe liver injury approximately two months after Saibokuto administration, necessitating steroid pulse therapy for recovery. The literature search was conducted on February 15, 2023 in Japan. Using PubMed and the "Igaku Chuo Zasshi (ICHUSHI) database," two individuals independently selected studies published between January 1997 and February 15, 2023. The search focused on studies involving human subjects, published in either English or Japanese, and specifically investigated Kampo medicines categorized as over-the-counter or prescription drugs suspected as causative agents of drug-induced liver injury (DILI). Studies on health supplements, discontinued Kampo medicines, and autoimmune hepatitis, were excluded. As it is ethically impossible to rechallenge drugs that cause liver injury, this review primarily relied on case report literature. Through the review, 37 cases (men/women: 12/25, including present case) were analyzed, including 32 reports (36 cases) from 3,055 studies that met the inclusion criteria. Notably, 65.9% of cases were associated with Scutellariae radix, with onset occurring within 45 (1-730) days and recovery within 35 (7-184) days. Our case study and literature review underscore a prevalent association between liver injury and Kampo medicines containing Scutellariae radix. Vigilant liver function monitoring, particularly within the first 2 months of administration, is recommended, especially for formulations containing Scutellariae radix.

DOI: 10.5582/ddt.2024.01087
PMID: 39756858 [Indexed for MEDLINE]

6. **Developing a Screening Strategy to Identify Hepatotoxicity and Drug Interaction Potential of Botanicals**. J Diet Suppl. 2025;22(1):162-192. doi: 10.1080/19390211.2024.2417679. Epub 2024 Oct 25.

   Roe AL, Krzykwa J, Calderón AI, Bascoul C, Gurley BJ, Koturbash I, Li AP, Liu Y, Mitchell CA, Oketch-Rabah H, Si L, van Breemen RB, Walker H, Ferguson SS.

   Botanical supplements, herbal remedies, and plant-derived products are used globally. However, botanical dietary supplements are rarely subjected to robust safety testing unless there are adverse reports in post-market surveillance. Botanicals are complex and difficult to assess using current frameworks designed for single constituent substances (e.g. small molecules or discrete chemicals), making safety assessments costly and time-consuming. The liver is a primary organ of concern for potential botanical-induced hepatotoxicity and botanical-drug interactions as it plays a crucial role in xenobiotic metabolism. The NIH-funded Drug Induced Liver Injury Network noted that the number of botanical-induced liver injuries in 2017 nearly tripled from those observed in 2004-2005. New approach methodologies (NAMs) can aid in the rapid and cost-effective assessment of botanical supplements for potential hepatotoxicity. The Hepatotoxicity Working Group within the Botanical Safety Consortium is working to develop a screening strategy that can help reliably identify potential hepatotoxic botanicals and inform mechanisms of toxicity. This manuscript outlines the Hepatotoxicity Working Group's strategy and describes he assays selected and the rationale for the selection of botanicals used in case studies. The selected NAMs evaluated as a part of this effort are intended to be incorporated into a larger battery of assays to evaluate multiple endpoints related to botanical safety. This work will contribute to a botanical safety toolkit, providing researchers with tools to better understand hepatotoxicity associated with botanicals, prioritize and plan future testing as needed, and gain a deeper insight into the botanicals being tested.

   DOI: 10.1080/19390211.2024.2417679
   PMID: 39450425 [Indexed for MEDLINE]

7. **Underreporting Supplements: A Case of Drug-induced Liver Injury Due to a Testosterone Booster.** Mil Med. 2025 Jan 16;190(1-2):e453-e455. doi: 10.1093/milmed/usae136.

   Manhas A(1), Arnold CG(1), Bush AM(2).

   Acute liver injuries (ALIs) are caused by a wide range of etiologies, and determining the cause can often be challenging. Detailed history taking is essential in patients with liver injuries to promptly determine the underlying source of injury and for timely treatment and prognosis. A 27-year-old active duty man presented to the emergency department (ED) with jaundice. On medication reconciliation, he only reported taking acetaminophen for a recent upper respiratory infection. The patient had an ALI and was treated with N-acetyl cysteine for presumed acetaminophen toxicity. Initially, his liver-associated enzymes (LAEs) improved, but 2 weeks after discharge, he returned to the ED upon referral from ship medical for jaundice and worsening liver injury. Repeated query into the patient's history revealed that he was using a testosterone booster supplement for 6 months preceding initial hospitalization. After evaluation of other etiologies for liver injury returned negative, drug-induced liver injury from

the testosterone booster was determined to be the underlying etiology. With discontinuation of the supplement, his liver injury improved. Hepatotoxicity is a major concern in supplement use; however, it is largely underreported. Supplements are often not recognized or reported as medications by patients, leading to failure to identify them as potential toxicants. This case highlights the importance of including supplement education and questioning in the evaluation of ALI and maintaining a high index of suspicion when other common etiologies of liver disease are negative.

DOI: 10.1093/milmed/usae136
PMID: 38687644 [Indexed for MEDLINE]

8. **Dietary Supplement-Induced Hepatotoxicity: A Clinical Perspective**.
J Diet Suppl. 2025;22(1):58-77. doi: 10.1080/19390211.2024.2327546. Epub 2024

Carty J(1), Navarro VJ(1).

The consumption of dietary supplements (DS) has resulted in a significant and escalating number of cases involving liver injury. It is crucial for clinicians and consumers to be well informed about the adverse effects of such products, leading to their discontinuation and timely reporting of any harmful cases. This article delves into the clinical perspective of DS-related hepatotoxicity, highlighting key concepts such as a systematic diagnostic approach. The discussion extends to notable examples of both currently popular and potential future dietary supplements, such as garcinia cambogia, turmeric, and ashwagandha, accompanied by an overview of recent findings. Causality assessment tools play a crucial role in establishing a connection between these products and instances of liver injury, with consideration of the advantages and disadvantages associated with their use. Fostering a comprehensive understanding of regulatory standards, coupled with a solid foundation of knowledge of DS, will prove instrumental in preventing DS-related hepatotoxicity. Achieving this goal requires collaborative efforts from both consumers and clinicians.

DOI: 10.1080/19390211.2024.2327546
PMID: 38528750 [Indexed for MEDLINE]

9. **Biochemical biomarkers for the toxicity induced by Traditional Chinese Medicine: A review update**. J Ethnopharmacol. 2025 Feb 11;341:119315. doi: 10.1016/j.jep.2024.119315. Epub 2025 Jan 2.

Gu X, Zou Y, Huang Z, Wei M, Ji L.

ETHNOPHARMACOLOGICAL RELEVANCE: Traditional Chinese medicine (TCM) is widely used in China for disease treatment and has become a valuable resource for drug development due to its high efficacy and low risk of side-effects. However, growing toxicity reports has garnered significant global attention. A major challenge in addressing TCM-induced toxicity is lack of specific and sensitive biomarkers for diagnosing and predicting its toxicity. Identifying toxicological biomarkers reflecting TCM-induced toxicity is crucial for timely detection and intervention, and provides significant clues for elucidating the underlying toxic mechanism and key target.

AIM OF THE STUDY: This article aims to summarize and classify some potential toxicological biomarkers for side-effects induced by TCM and its contained phytochemical ingredients.
METHODS: The keywords "biomarkers", "traditional Chinese medicine", "Chinese herb", "phytochemical ingredient", "natural product", "toxicity", "hepatotoxicity", nephrotoxicity", "cardiotoxicity" were used to collect relevant information from literature databases (including PubMed, Web of Science) up to October 2024.
RESULTS: Research has indicated that more sensitive and specific biomarkers are needed for reflecting TCM's side-effects. PA-protein adducts and AA-DNA adducts could be served as diagnostic biomarkers for hepatotoxicity and nephrotoxicity induced by TCM containing PA and AA, respectively. Multiple miRNAs like miRNA-122-3p, miRNA-5099, and miRNA-21-3p, as well as some endogenous metabolites such as hypoxanthine, choline, and L-valine could be potential biomarkers associated with TCM-induced hepatotoxicity, nephrotoxicity, and cardiotoxicity.
CONCLUSION: In this review, different research demonstrates that DNA/protein-adducts, noncoding RNAs, endogenous metabolites and so on show the potential to be new early-warning biomarkers for TCM-induced toxicity with high specificity and sensitivity.

DOI: 10.1016/j.jep.2024.119315
PMID: 39755183 [Indexed for MEDLINE]

10. **Toxicological investigation of 25 aconitine-induced deaths from 2005 to 2023**. Leg Med (Tokyo). 2025 Feb;72:102564. doi: 10.1016/j.legalmed.2024.102564. Epub 2024 Dec 19.

Wang X, Wang X, Liu W, Chen H, Zhang Z, Zhao Y, Xiang P.

Aconitum herbs contain several highly toxic diester-diterpenoid alkaloids, including aconitine, mesaconitine, and hypaconitine. However, finding the cause of death is rather difficult for forensic pathologists during forensic autopsy of aconitine-induced death. Therefore, the ability to determine Aconitum alkaloids is important in these cases. The aim of this study was to review the data for alkaloids in postmortem specimens from 25 aconitine-induced deaths received by the Academy of Forensic Science from 2005 to 2023. Aconitum alkaloids were analyzed using an LC-MS/MS method, which was validated for blood, urine, and liver tissue. Briefly, 0.5 mL (g) of biological sample was subjected to liquid-liquid extraction with diethyl ether at pH 9.2. In 25 aconitine-induced deaths, the blood levels of aconitine, mesaconitine, and hypaconitine were 2.9-470 ng/mL (n = 22), ＜LOQ-30 ng/mL (n = 10), and ＜LOQ-5.0 ng/mL (n = 10), respectively. In some cases, other biological samples (e.g., urine, gastric contents, and liver tissue) and the materials seized on site (e.g., homemade medicinal liquor) were also analyzed. A significant positive correlation was observed between the biological samples and the seized materials for the concentration ratios of aconitine to mesaconitine and of aconitine to hypaconitine. The risk of aconite poisoning is increased by inappropriate administration, including drinking of homemade medicinal liquors containing Aconitum alkaloids, the use of unprocessed or improperly processed Aconitum plant material, and excessive consumption or misuse without doctors' directions. Accidental death caused by misuse of herbal drugs was the main cause of death in the 25 aconitine-induced deaths studied here.
DOI: 10.1016/j.legalmed.2024.102564
PMID: 39746252 [Indexed for MEDLINE]

11. **Unveiling the impact of traditional Chinese herbal medicines on cutaneous adverse drug reactions: A landmark 15-year nationwide study**. Phytomedicine. 2025 Jan;136:156273. doi: 10.1016/j.phymed.2024.156273. Epub 2024 Dec 1.

    He S, Yang J, Yang F, Chen S, Chen Z, Wang L, Gao H, TangC, Guan C, Zhang L, Gu Q, Luo X

    BACKGROUND: Traditional Chinese herbal medicines (TCMs) have become increasingly integrated into global healthcare systems, often used alongside conventional pharmaceuticals. While TCMs offer therapeutic benefits, their concomitant use with other medications raises concerns over cutaneous adverse drug reactions (CADRs). Despite the widespread use of TCMs, large-scale studies examining their safety in combination with antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs) remain limited.
    OBJECTIVE: This study aimed to analyze the frequency and severity of CADRs associated with TCMs, focusing on their interactions with antibiotics and NSAIDs in a comprehensive dataset spanning over 15 years in China.
    METHODS: We retrospectively reviewed clinical data from over 1.8 million patient visits annually between 2007 and 2022. Both mild and severe CADRs (SCARs) associated with TCMs, antibiotics, and NSAIDs were evaluated.
    RESULTS: While used in combination with antibiotics or NSAIDs, TCMs did not significantly increase the incidence of SCARs, although TCMs, antibiotics, or NSAIDs accounted for a proportion of CADRs. In contrast, the combination of antibiotics with NSAIDs showed a higher frequency of SCARs compared to monotherapy. These results suggest that TCMs have a favorable safety profile in multi-drug regimens, but careful monitoring is essential, particularly in multi-drug therapies involving conventional medications.
    CONCLUSION: This groundbreaking study provides unprecedented insights into the role of TCMs in CADRs, highlighting their potential for safer integration into multi-drug regimens. Although TCMs did not exacerbate the risk of severe reactions when combined with antibiotics or NSAIDs, vigilance in drug safety protocols remains crucial. These findings support the cautious and well-regulated use of TCMs within broader healthcare frameworks, promoting their safe integration alongside conventional therapies.

    DOI: 10.1016/j.phymed.2024.156273
    PMID: 39644761 [Indexed for MEDLINE]

12. **Dietary Supplement Safety in Older Adults: A Review of Published Case Reports**. Sr Care Pharm. 2025 Jan 1;40(1):32-49. doi: 10.4140/TCP.n.2025.32.

    Shahverdian A, Jafari M.

    Objective: This review summarizes recent case reports where the consumption of dietary supplements by older adults may have caused an adverse event. Data Sources: In December 2023, PubMed was surveyed for case reports published from 2000 onwards, using two medical subject heading (MeSH) terms, "aged" and "dietary supplements," where the latter was combined with the MeSH subheadings "adverse effects," "poisoning," or "toxicity." Major clinical trials for dietary supplements were identified at <ext-link ext-link-type="uri" xlink:href="https://ClinicalTrials.gov">ClinicalTrials.gov</ext-link>, an online database of

clinical research studies, or in PubMed, and screened for information on adverse effects. Data Synthesis: The described search strategy yielded 820 publications, including 122 case reports, which were then manually screened for relevant and informative case reports involving dietary supplements and people 65 years of age or older. Consequently, 41 publications were selected describing 46 individual case reports. Etiologies of adverse events included interactions of dietary supplements with prescribed medication, ingestion of higher-than-intended or instructed supplement doses, intake of the same supplement from multiple sources, and supplement contamination. Prominent adverse events encompassed hypercalcemia (vitamin D), thyroid test interference (vitamin B7), neuropathy (vitamin B6), oxalate nephropathy (vitamin C), and interactions with warfarin therapy (vitamins E and K, and omega-3 fatty acids). Conclusion: Health care practitioners are advised to consider dietary supplements as contributors to adverse clinical symptom presentations, while patients are encouraged to provide current records of their prescribed medications and dietary supplements to their health care providers. This is particularly important for older adults where both medication intake and supplement consumption are high.

DOI: 10.4140/TCP.n.2025.32
PMID: 39747809 [Indexed for MEDLINE]

13. **Toxicity Potential of Nutraceuticals**. Methods Mol Biol. 2025;2834:197-230. doi: 10.1007/978-1-0716-4003-6_10.

    Gupta RC, Doss RB.

    During the past few decades and especially during and after the COVID-19 pandemic, the use of nutraceuticals has become increasingly popular in both humans and animals due to their easy access, cost-effectiveness, and tolerability with a wide margin of safety. While some nutraceuticals are safe, others have an inherent toxic potential. For a large number of nutraceuticals, no toxicity/safety data are available due to a lack of pharmacological/toxicological studies. The safety of some nutraceuticals can be compromised via contamination with toxic plants, metals, mycotoxins, pesticides, fertilizers, drugs of abuse, etc. Knowledge of pharmacokinetic/toxicokinetic studies and biomarkers of exposure, effect, and susceptibility appears to play a pivotal role in the safety and toxicity assessment of nutraceuticals. Interaction studies are essential to determine efficacy, safety, and toxicity when nutraceuticals and therapeutic drugs are used concomitantly or when polypharmacy is involved. This chapter describes various aspects of nutraceuticals, particularly their toxic potential, and the factors that influence their safety.

    DOI: 10.1007/978-1-0716-4003-6_10
    PMID: 39312167 [Indexed for MEDLINE]

14. **Drug reaction with eosinophilia and systemic symptoms with toxic epidermal necrolysis like rash in systemic sclerosis and overlapping sjogren's syndrome: A double trouble triggered by a herbal medicine**. Indian J Dermatol Venereol Leprol. 2024 Dec 7:1-3. doi: 10.25259/IJDVL_726_2024.

    Youvalakshmi S(1), Logamoorthy R(1), Karthikeyan K(1).

    DOI: 10.25259/IJDVL_726_2024
    PMID: 39912181

15. **Mexican calea (Calea zacatechichi Schltdl.) interferes with cholinergic and dopaminergic pathways and causes neuroglial toxicity**. J Ethnopharmacol. 2025 Jan 30;337(Pt 3):118915. doi: 10.1016/j.jep.2024.118915. Epub 2024 Oct 9.

    Garcia MR(1), Ferreres F(2), Mineiro T(3), Videira RA(4), Gil-Izquierdo Á(5), Andrade PB(6), Seabra V(7), Dias-da-Silva D(8), Gomes NGM(9).

    ETHNOPHARMACOLOGICAL RELEVANCE: The use of "Mexican calea" (Calea zacatechichi Schltdl.) in ritualistic ceremonies, due to its dream-inducing effects, was until recently limited to indigenous communities in Mexico. However, the plant has recently gained popularity in Western societies being commonly used in recreational settings. Despite the traditional and recreational uses, mechanisms underlying its reported oneirogenic effects remain unknown, with no data available on its neurotoxic profile.
    AIM OF THE STUDY: The scarcity of toxicological data and the unknown role of major neurotransmitter systems in the dream-inducing properties of the plant prompted us to investigate which neurotransmitters might be affected upon its consumption, as well as the potential cytotoxic effects on neurons and microglial cells. Furthermore, we aimed to explore a relationship between the recorded effects and specific constituents.
    MATERIALS AND METHODS: Effects on cholinergic and monoaminergic pathways were investigated using enzymatic assays, with the latter also being conducted in neuronal SH-SY5Y cells along with the impact on glutamate-induced excitotoxicity. Investigation of the neurotoxic profile was approached in neuronal SH-SY5Y and microglial BV-2 cells, evaluating effects on metabolic performance and membrane integrity using MTT and LDH leakage assays, respectively. Potential interference with oxidative stress was monitored by assessing free radical's levels, as well as 5-lipoxygenase mediated lipid peroxidation. Phenolic constituents were identified through HPLC-DAD-ESI(Ion Trap)MSn analysis.
    RESULTS: Based on the significant inhibition upon acetylcholinesterase ($p < 0.05$) and tyrosinase (IC50 = 60.87 ± 7.3 μg/mL; $p < 0.05$), the aqueous extract obtained from the aerial parts of C. zacatechichi interferes with the cholinergic and dopaminergic systems, but has no impact against monoamine oxidase A. Additionally, a notable cytotoxic effect was observed in SH-SY5Y and BV-2 cells at concentrations as low as 125 and 500 μg/mL ($p < 0.05$), respectively, LDH leakage suggesting apoptosis may occur at these concentrations, with necroptosis observed at higher ones. Despite the neurocytotoxic profile, these effects appear to be independent of radical stress, as the C. zacatechichi extract scavenged nitric oxide and superoxide radicals at concentrations as low as 62.5 μg/mL, significantly inhibiting also 5-lipoxygenase (IC50 = 72.60 ± 7.3 μg/mL; $p < 0.05$). Qualitative and quantitative analysis using HPLC-DAD-ESI(Ion Trap)MSn enabled the identification of 28 constituents, with 24 of

them being previously unreported in this species. These include a series of dicaffeoylquinic, caffeoylpentoside, and feruloylquinic acids, along with 8 flavonols not previously known to occur in the species, mainly 3-O-monoglycosylated derivatives of quercetin, kaempferol, and isorhamnetin
CONCLUSIONS: Our findings regarding the neuroglial toxicity elicited by C. zacatechichi emphasize the necessity for a thorough elucidation of the plant's toxicity profile. Additionally, evidence is provided that the aerial parts of the plant inhibit both acetylcholinesterase and tyrosinase, potentially linking its psychopharmacological effects to the cholinergic and dopaminergic systems, with an apparent contribution from specific phenolic constituents previously unknown to occur in the species. Collectively, our results lay the groundwork for a regulatory framework on the consumption of C. zacatechichi in recreational settings and contribute to elucidating previous contradictory findings regarding the mechanisms underlying the dream-inducing effects of the plant.

DOI: 10.1016/j.jep.2024.118915
PMID: 39389391 [Indexed for MEDLINE]

16. **A comprehensive review on pharmacokinetic mechanism of herb-herb/drug interactions in Chinese herbal formula.** Pharmacol Ther. 2024 Dec;264:108728. doi: 10.1016/j.pharmthera.2024.108728. Epub 2024 Oct 9.

Li M, Wang Y, Chen Y, Dong L, Liu J, Dong Y, Yang Q, CaiW, Li Q, Peng B, Li Y, Weng X, Wang Y, Zhu X, Gong Z, Chen Y.

Oral administration of Chinese Herbal Medicine (CHM) faces various challenges in reaching the target organs including absorption and conversion in the gastrointestinal tract, hepatic metabolism via the portal vein, and eventual systemic circulation. During this process, factors such as gut microbes, physical or chemical barriers, metabolic enzymes, and transporters lay crucial roles. Particularly, interactions between different herbs in CHM have been observed both in vitro and in vivo. In vitro, interactions typically manifest as detectable physical or chemical changes, such as facilitating solubilization or producing precipitates when decoctions of multiple herbs are administered. In vivo, such interactions cause alterations in the ADME (absorption, distribution, metabolism, and excretion) profile on metabolic enzymes or transporters in the body, leading to competition, antagonism, inhibition, or activation. These interactions ultimately contribute to differences in the therapeutic and pharmacological effects of multi-herb formulas in CHM. Over the past two thousand years, China has cultivated profound expertise and solid theoretical frameworks over the scientific use of herbs. The combination of multiple herbs in one decoction has been frequently employed to synergistically enhance therapeutic efficacy or mitigate toxic and side effects in clinical settings. Additionally combining herbs with increased toxicity or decreased effect is also regarded as a remedy, a practice that should be approached with caution according to Traditional Chinese Medicine (TCM) physicians. Such historical records and practices serve as a foundation for predicting favorable multi-herb combinations and their potential risks. However, systematic data that are available to support the clinical practice and the exploration of novel herbal formulas remain limited. Therefore, this review aims to summarize the pharmacokinetic interactions and mechanisms of herb-herb or herb-drug combinations from

existing works, and to offer guidance as well as evidence for optimizing CHM and developing new medicines with CHM characteristics.

DOI: 10.1016/j.pharmthera.2024.108728
PMID: 39389315 [Indexed for MEDLINE]

17. **Increased risk of major adverse cardiovascular events in young and middle-aged adults with obesity receiving Chinese herbal medicine:** A nationwide cohort study. J Chin Med Assoc. 2024 Dec 1;87(12):1031-1038. doi: 10.1097/JCMA.0000000000001163. Epub 2024 Sep 13.

Yang WC(1), Weng TI(2)(3), Shih YH(4), Chiu LT(4).

BACKGROUND: Many patients with obesity in Taiwan seek Chinese herbal medicines (CHM) from traditional Chinese medicine (TCM) clinics. This study aimed to estimate the risk of major adverse cardiovascular events (MACEs) in adults diagnosed with obesity, with or without CHM.METHODS: Patients with obesity aged 18 to 50 years were identified using diagnostic codes from Taiwan's National Health Insurance Research Database between 2008 and 2018. We randomized 67 655 patients with or without CHM using propensity score matching. All patients were followed up from the start of the study until MACEs, death, or the end of 2018. A Cox proportional regression model was used to evaluate the hazard ratios of MACEs in the CHM and non-CHM cohorts.RESULTS: During a median follow-up of 4.2 years, the CHM group had a higher incidence of MACEs than the non-CHM control cohort (9.35 vs 8.27 per 1000 person-years). The CHM group had a 1.13-fold higher risk of MACEs compared with the non-CHM control (adjusted hazard ratio [aHR] = 1.13; 95% CI], 1.07-1.19; $p < 0.001$), especially in ischemic stroke (aHR = 1.18; 95% CI, 1.07-1.31; $p < 0.01$), arrhythmia (aHR = 1.26; 95% CI, 1.14-1.38; $p < 0.001$), and young adults aged 18 to 29 years (aHR = 1.22; 95% CI, 1.05-1.43; $p < 0.001$).CONCLUSION: Although certain CHMs offer cardiovascular benefits, young and middle-aged obese adults receiving CHM exhibit a higher risk of MACEs than those not receiving CHM. Therefore, TCM practitioners should be cautious when prescribing medications to young patients with obesity, considering their potential cardiovascular risks.

DOI: 10.1097/JCMA.0000000000001163
PMID: 39267390 [Indexed for MEDLINE]