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Toxicokinetics and Molecular Targets of Herb-Drug Interactions

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Abstract. This review focus on the impact of Chinese herbal medicine on most of the body systems in animals and humans. There are advantages and drawbacks in Traditional Chinese Medicines (TCMs), since different dosages and types of active ingredients in TCM could cause different extents of side effects and cure certain diseases at the same time. Common side-effects include liver and kidney damage, allergic reaction, increase the possibility of bleeding, and some might contain heavy metals such as lead and arsenic; some study also proven to cause central nervous system. Nevertheless, taking TCM with proper and precise dosage could indeed reduce stress, enhance sleeping quality, and balance the hormones to regulate women's menstrual cycle. In this paper, herbs used include Fuzi, aristolochic acid, Pyrrolizidine alkaloids, Banaba, and ginseng. These are the main herbs that will be discussed. their properties and side-effects will be explained and methods used to track how toxic is produced will be demonstrated. Overall, this review aims to identify the actual damage toxins in herbs have on the central nervous system and body systems, and mechanisms causing damage as well as risk management to control the dosage to ensure it reaches maximum benefits with the least side effects.

Keywords: Banaba; pyrrolizidine alkaloids; ginseng; Traditional Chinese Medicine.

1. Introduction

Traditional Chinese medicine (TCM) was made using herbs, and the history of herbs dates back around 2200 years. This practice and wisdom were built starting from the 3rd century BCE by the renowned Yellow Emperor's Inner Canon. Traditional herbalists believed that the body exists a natural life force known as "qi" which could connect organs, tissues, veins, nerves, cells, atoms, and consciousness, and this particular life force flows through the body by invisible channels in the body called meridians. It is also regarded that there are two complementary forces in the body, which are called yin and yang. The former being passive and the latter being active maintains a dynamic equilibrium within the body, and when this balance is fluctuating or falling to one side, TCM is thus used to balance it [1].

Acknowledging the mechanisms in curing disease and pain, it is crucial that in detail TCM could help reduce inflammations in the body as well as preventing and treating diabetes, cancer, or heart diseases. As an exemplary, curcumin found in the rhizome of turmeric plant sets a great example of detoxification and anti-inflammations. It does this by eliminating free radicals which could cause endothelial cell damage and eventually lead to CVD or CHD. Ginseng and Banaba in this case could also help to combat with oxidative stress by neutralizing excessive oxygen species such as ROS and protects heart and brain cells from apoptosis, it also allows the level of antioxidants enzymes to increase like the superoxide dismutase and catalase. Regardless of the benefits, herbs also exist natural toxins that endanger the body of human or animals. This is mainly done by previously explained oxidative stress, mitochondrial dysfunction, membrane disruption, DNA adduct formation and genotoxicity. Some damage are also caused by intaking herbs containing heavy metals [2].

2. Different Mechanisms

First and foremost, after the entry of the herbs into the human or animal body, two terminologies are involved during the dissection of the TCM. These are the pharmacodynamic and pharmacokinetic herb-drug interactions. Which the former refers to the study on how the drug does to the body. It

includes three main perspectives, which are viewing from a biochemical, physiological, and molecular level. The later on the other hand refers to how the drug is treated by the body, also called the ADME interactions [3].

Secondly, the nephrotoxicity induced by Aristolochic Acid has its specific molecular mechanisms and protective approaches. Essentially, the mechanisms are initially triggered by the nitrotreduction of AAI and AAII leading to related N-hydroxyaristolactams which will be converted into aristolactam nitrenium ion. It is an reactive species that can react with exocyclic amino groups, specifically the purine bases of DNA to produce DNA-adducts. These DNA conjugates will eventually lead to the mutation of TP53, which leads to nephrotoxicity or cancer if worse [4].

Besides the mechanism illustrated by this figure, molecular processes engaged in AA-evoked nephrotoxicity could also explain the cause and effect leading to nephrotoxicity. Firstly, products of cellular metabolism, such as nitrogen species and reactive oxygen, play crucial roles in signal transmission and equilibrium in body. However, producing ROS and NOS excessively or the exhaustion of it could both lead to redox imbalance. Besides endogenous mechanisms, various xenobiotics could also induce oxidative stress, causing cell impairment, with AA being one of the xenobiotics.

A study focusing on this has been conducted, and Yu and colleagues have found that DNA damage is caused by the activation of the mitogen-activated protein kinase signaling route and the reduction of intracellular glutathione. AA can also induce apoptosis and cell arrest in the G2 and M phase via the sythesis of reactive oxygen species and the activation of mitogen-activated protein kinase. Through observation, MAP kinase could activate p38, causing cell death. Redox imbalance linking with inflammations was also observed when using a mouse model of AA-induced acute kidney injury [4].

3. Herbs and Their Active Components

In the previous sections, mechanisms have been explained, and therefore this section's approach is more about listing examples that have correlations to the mechanisms and explaining using experiments and figures to identify toxins and possible methods to treat the disease led by TCMs.

3.1. Pyrrolizidine Alkaloids (PAs)

PA are natural toxins that exhibit genotoxicity, hepatoxicity, and carcinogenicity. They are mostly presented in food and herbal products. PAs are secondary metabolites produced by plants to defend against herbivores. According to the report, around 660 PAs N-oxides of them prescence in over 6000 plants distributed across the world, make up 3 percent of all flowering plants. PAs are made up of a 1-hydroxylmethyl linked to an aliphatic monocarboxylic or dicarboxylic acid, depending on whether one or both hydroxyl groups are esterified, they can be classified as monoesters or diesters. Cyclical diester results from the esterification with two carboxyl groups of a dicarboxylic acid. Based on structural differences, 1,2-unsaturated PAs can be classified into one diastereometric form of the necine base, the other diastereometric form, or a structurally different third class; among these, necine base of retronecine and heliotridine are diastereomers due to the different layout of the seventh carbon atom in the ring system. Hepatotoxicity is thought to be strengthened by esterification of the hydroxyl groups at carbon-7. Hence, the toxicity is highly correlated with its chemical structure. Weak to strong toxic effects are arranged from monoesters, open-chain diesters of 1,2-unsaturated PAs, and cyclic diesters. So the formation of a cyclic diester is the esterification of two carboxyl groups of a dicarboxylic acid.

Furthermore, exposure to PAs in the long term could lead to hepatic veno-occlusive disease and human hepatic sinusoid occlusion syndrome. It is acknowledged that PAs itself isn’t toxic, but the toxicity is caused by hepatic cytochrome P450, linked to the metabolic activation [5].

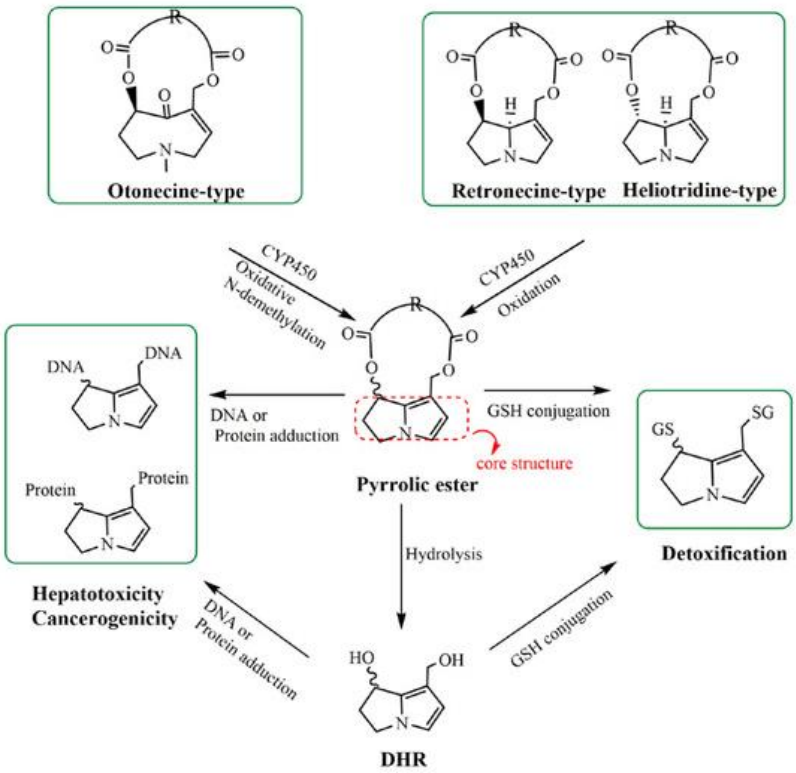

Figure 1. Metabolic activation of retronecine-, heliotridine-, and otonecine-type PAs leading to hepatotoxicity and tumorigenicity, and detoxification [5].

Figure 1 shows the three types of PAs that could be transformed into 6,7-dihydro-7-hydroxy-1-hydroxymethyl-5H-pyrrolizidine (DHP) esters. DHP ester continuely could be hydrolyzed to yield DHP. These pyrrole metabolites are chemically very active, bifuntional alkylating agents that once formed can react with nucleophilic groups in DNA and cellular proteins, while also causing DNA binding, cross-linking, and DNA protein cross-linking. These effects eventually lead to hepatoxicity, genotoxicity and carcinogenicity. DHP, which is closely related to DHP esters, is also capable of binding to glutathione, proteins, and DNA, forming pyrrole-GSH adducts, pyrrole-DNA adducts, and pyrrole-protein adducts; these products also induce the same toxic effect [5].

3.2. Fuzi

Fuzi is a processed lateral root of Aconitum carmichaelii Deb, it is the components in more than 60 popular traditional Chinese formulae and it is used to treat rheumatism arthritis, cardiovascular diseases and bronchitis in many Asian countries.

Regardless of the therapeutic effects, it also has toxicities. It has been reported that there are around 5000 cases of aconite poisoning worldwide between 2001 and 2010, and 41 cases more between 2012 and 2017. However, the active ingredients was actually not complicated. The essense of the toxin is caused by the three main carbon 19-diester-diterpenoid alkaloids (DDAs) and the primary bioactive ingredients in aconite roots are DDAs, aconitine (AC), mesaconitine (HA), which are believed to be the main toxic components causing damage. The toxicity is primarily cardiotoxicity, liver damage and kidney damages. It does this by elevating cardiac enzymes, myocardial necrosis. The liver damage is caused by elevating necrosis in hepatic tissue and edema and kidney is elevated by atrophy and lymphocyte infiltration in renal tissue. So essentially the mechanism is that the AC will bind with a super high affinity to sodium channels in cardial myocytes, it will keep them open and lead to an excessive sodium influx and cause calcium to overload using perturbation of the sodium and calcium exchange system. The downregulation of the endoplasmic reticulum calcium ATPase causing ionic disturbances which can trigger arrhythmias and cell death.

Experiments was done using pre-clinical models to test for the toxicity in addition. Median lethal dose (LD50), commanly implemented for assessing toxicity of fuzi and DDAs. the results have shown that the the mice with DDAs has a LD50 value of 1.8 miligrams but it was a 1000-fold less for a mice with MDAs. Thus DDAs toxicity effect is the highest among all three of the carbon 19 diester diterpenoid alkaloids [6].

3.3. Herbs-Inducing Liver Injury

Herb-induced liver injury can be caused by many factors, these damages could be originally presented in supplements and natural products. A majority of herbal products have components from different plant parts. It could be made to various forms such as tea, powder, oils, creams, or capsules. In this section, a clear procedure are used to lead to a sensible diagnosis of herb-induced liver injury.

Hepatotoxicity initial assessment was first introduced to notify if the liver enzymes have increased beyond the upper limit of ULN of ALT and ALP. Nevertheless, the value above ULN that are considered toxic has distinction with the references [7].

In recent studies, more findings shed lights into the field of herbs-induced liver injury. It is astonishing that it is actually the indirect hepatotoxicity which is the derivatives of drugs or herbs toxification, besides parent drug or herb. It is obvious that the response of immune system is abnormal and is often involved in injuries alike. HILI in this type are caused by E.brevicornu and P.corylifolia, these two herbs are known for their power to benefit the immune response system. Recent studies also indicates that eventhough both of these induce liver injury in animals, NLRP3 inflammasome and trigger abundant release of waster products of immune-activating cytokines in endotoxin in weakly-stimulated animals could all be activated [8].

4. Protective TCMs and Methods to Analyze Toxicity

4.1. Ginsengs and Banaba

This section investigates whether both of these extracts have any protective effect on top of fluoride intoxication and diabetes.

Firstly, ginseng and banaba is the root and leaf extract that are commonly used in many regions around the globe. In traditional chinese medicine, they are vital when treating hyperglycemia. The main active component serving function is called triterpinoid and saponin glycosides. These are mainly found in India, Philippine, southern China, and Malaya. The combination of mulberry, korean red ginseng, banaba, and anti-diabetic drugs are shown to have lower the sensitivity of insulin, and improving hyperglycaemia and elevation on peroxisome proliferator-activated receptors expression by facilitating the oxidation of mitochondria and increase the absorption of free fatty acids, thus, decreasing the blood glucose level indirectly. The in vivo testing in rats have shown the likelihood of diminishing flouride and inhibiting the toxins in flouride. Present study pinpoints on the impact of ginseng and banaba on the mitochondrial redox imbalance in mice with STZ induced diabetes and toxins in flouride.

The method and materials include a standardized root solution and extract of ginseng (having 80% of ginsenosides) and banaba (containing one percent of corosolic acid fraction). Chemicals obtained includes Streptozotocin, 5,5’-Dithio-bis(2-nitrobenzoic-acid) and 1-chloro-2,4-dinitrobenzene. Animals include adult albino mice, Mus musculus(3 month old), the mass of it is 30 plus or minus 5g. The experiment was designed to have groups and each with 6 mice. One control group given regular tap water. Group 2 with one single dose of STZ and diabetes were confirmed after 7 days. Group 3 received 600 ppm of sodium fluoride in drinking water. Group 4 act as an advantageous control and on the 7th day of confirming the induced diabetes with blood glucose larger than 200mg/dL, those animals were treated with 600 ppm of sodium flouride by drinking waters for 30 days. These animals were then separated into groups to examine for effectiveness of plant extracts, BLE and GE, having an exposure isolated and both of 15 days. Group 5 to 7 had phytochemical

preparation supplemented experimental mice at a range of dose (50,150,250mg/kg b.w./day) while sustaining the F exposure. By the end of day 52, tail vein puncture was put into practice to collect blood and all the animal in the test and control group were required to have there spine dislocated and dissecting the kidney out. One kidney was taken for microscopic tissue evaluation and for flouride content estimation, with the other one being washed in cold saline, it is for to homogenize and subject to organelle isolation to acquire mitochondrial fraction for biochemical analysis. The mass of the body was measured prior the therapy, it is done recurringly and every optional day and 15th day. The weight of different groups was recorded and organo-somatic index was calculated by the formula:

Weight of organ divide the total body weight, both calculated in grams.

Therefore, this experiment was conducted to notify the alterations and impact the two extracts had on the mice in control and groups with drugs taken. Results came out and shown that the value of OSI has declined significantly compared to the group without taken the dosage of STZ,F and STZ + F. Therefore, it is proven that ginseng and banaba both or alone could help the value of OSI to restore to a normal range [9].

4.2. Sodium Formononetin-3'-Sulphonate and Toxin Examination

Sul-F is a novel agent that has a good aqueous solubility and strong activity. Studies done before have shown that it does not only like water but also great at lowering lipids and protects the liver well. The possibility of genotoxicity of Sul-F was evaluated utilizing bacterial reverse mutation test, chromosomal aberrations detection, and mouse micronucleus test.

During bacterial reverse mutation test, five variant of salmonella typhimurium, Sul-F(250,500,1000,2000,4000μg/plate) weren't able to promote the size of the restored outgrowths in any tester variant without or with S9 mix. The lung fibroblast cells of Chinese hamsters were utilized during chromosomal assay, no increase observed in neither type of aberration at different dose of Sul-F(400,800,1600μg/mL) treatment groups with or without S9 metabolic activation.

Last but not least, an in vivo bone marrow micronucleus test in ICR mice was conducted and Sul-F was increased to 2000mg/kg were showing no large increase in the frequency of micronucleated polychromatic erythrocytes, or any crucial changes in the proportion of under-developed red blood cells to total red blood cells [10].

5. Conclusion

This article systematically reviews the toxic reactions caused by TCM and its active ingredients, as well as related protective strategies. It focuses on analyzing the mechanisms of action and effects on vital organs of common TCM toxic components such as aristolochic acid, PAs, and aconite. Studies have shown that TCM toxicity mainly exerts its effects through oxidative stress, DNA damage, mitochondrial dysfunction, apoptosis, and inflammatory responses. Specifically, aristolochic acid can form DNA adducts and induce TP53 gene mutations, leading to nephrotoxicity and carcinogenic risk; pyrrolizidine alkaloids, after activation by liver metabolism, produce highly reactive metabolites, causing hepatotoxicity, genotoxicity, and tumorigenesis; and diester-type diterpenoid alkaloids in aconite mainly cause damage to the heart, liver, and kidneys by interfering with ion channel function. Meanwhile, multiple studies have found that extracts of TCMs such as ginseng and crape myrtle (Banaba) have antioxidant and toxic damage-mitochondrial-reducing effects, improving mitochondrial function and alleviating oxidative stress. Furthermore, modern toxicological evaluation methods such as bacterial reverse mutation assays, chromosome aberration assays, and micronucleus assays provide reliable evidence for TCM safety research. Future research should further integrate molecular biology, omics technology and precision toxicology research to elucidate the toxicity mechanisms of TCM, strengthen the construction of a safety evaluation system, and provide theoretical support for the scientific application of TCM and the development of new drugs.

References

[1] Britannica Editors. traditional Chinese medicine. Encyclopedia Britannica. 2026, May 27. https://www.britannica.com/science/traditional-Chinese-medicine.

[2] El-Saadony, M. T., Yang, T., Korma, S. A., et al. Impacts of turmeric and its principal bioactive curcumin on human health: Pharmaceutical, medicinal, and food applications: A comprehensive review. Frontiers in Nutrition. 2023, 9: 1040259. https://doi.org/10.3389/fnut.2022.1040259.

[3] Czigle, S., Nagy, M., Mladěnka, P., Tóth, J., OEMONOM. Pharmacokinetic and pharmacodynamic herb-drug interactions—Part I: Herbal medicines of the central nervous system. PeerJ. 2023, 11: e16149. https://doi.org/10.7717/peerj.16149.

[4] Anger, E. E., Yu, F., Li, J. Aristolochic acid-induced nephrotoxicity: Molecular mechanisms and potential protective approaches. International Journal of Molecular Sciences. 2020, 21(3): 1157. https://doi.org/10.3390/ijms21031157.

[5] Wang, J., Zhang, M., Chen, L., et al. Determination of toxic pyrrolizidine alkaloids in traditional Chinese herbal medicines by UPLC-MS/MS and accompanying risk assessment for human health. Molecules. 2021, 26(6): 1648. https://doi.org/10.3390/molecules26061648.

[6] Yang, M., Ji, X., Zuo, Z. Relationships between the toxicities of Radix Aconiti Lateralis Preparata (Fuzi) and the toxicokinetics of its main diester-diterpenoid alkaloids. Toxins. 2018, 10(10): 391. https://doi.org/10.3390/toxins10100391.

[7] Nunes, D. R. D. C. M. A., Monteiro, C. S. J., Dos Santos, J. L. Herb-induced liver injury—a challenging diagnosis. Healthcare (Basel). 2022, 10(2): 278. https://doi.org/10.3390/healthcare10020278.

[8] Ma, Z. T., Shi, Z., Xiao, X. H., Wang, J. B. New insights into herb-induced liver injury. Antioxidants & Redox Signaling. 2023, 38(16–18): 1138–1149. https://doi.org/10.1089/ars.2022.0134.

[9] Basha, M. P., Saumya, S. M. Influence of fluoride on streptozotocin-induced diabetic nephrotoxicity in mice: protective role of Asian ginseng (Panax ginseng) and banaba (Lagerstroemia speciosa) on mitochondrial oxidative stress. The Indian Journal of Medical Research. 2013, 137(2): 370–379.

[10] Li, C., Gao, Y., Wang, Y., et al. Genotoxicity testing of sodium formononetin-3'-sulphonate (Sul-F) by assessing bacterial reverse mutation, chromosomal aberrations and micronucleus tests. Regulatory Toxicology and Pharmacology. 2017, 86: 374–378. https://doi.org/10.1016/j.yrtph.2017.04.005.