

A critical insight of modern herbal drugs therapy under the purview of toxicity and authenticity.

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Abstract

Herbal medicines have recently been used for treatment of various diseases. The unwanted reaction and other concern like authenticity of herbal drugs is one of the important issues that have been addressed in this article. Toxicity of various important herbal drugs which are used regularly may also induce fatal reaction in our body. Herbal drug interaction with conventional drug and their serious consequences may be also life threatening for the patients who consume herbal drugs. Drug mutagenicity and contamination of herbal drugs are discussed here with suitable example. Drug authenticity with suitable illustration is also depicted in this review article. The aim of this article is to deliver an insight to the critical points of modern herbal drugs therapy and to find the scope for future scientists to overcome the serious issues regarding the herbal drugs treatment in recent era.

Keywords: Herbal drugs, Toxicity, Drug authenticity, Drug interaction.

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Introduction

The herbal therapy as mainline treatment becomes very popular among the huge percentage of population in America [1]. In addition, the government of UK in recent year spends £40 million for herbal treatment [2]. Due to its high efficacy against mild to life threatening disease, herb drugs have acquired a huge popularity among various populations throughout the world. The uses of herbal drugs are still very limited due to its enormous side effects. The side effects and adverse reaction of the herbal drugs are mainly manifested in various forms like allergic reaction, vomiting, itching, abdominal discomfort, etc. There are several herb medicines which have various narcotic derivatives that may cause various types of drug dependency as well as permanent damaging of central nervous system. In addition drug interaction for different category of herbal drugs may endanger the patients' health condition. For these reasons the World Health Organization (WHO) released several guidelines for agricultural plantation and collection procedure for medicinal herbs [3-9]. The main problem with medicinal plants is the quality of the raw form of the herbal medicine and the

selection of wrong species. Another problem of herbal drug is its cross contamination. Contamination of parent herbal drugs may happen intentionally. Accidental contamination is also possible which may cause serious consequences. The herbal drugs may have high concentration toxic metal including arsenic, mercury, cadmium. These metals may enter into the human body with various forms of herbal drugs and have serious deleterious effects in long term uses of those herbal drugs. The use of pesticides for cultivation of medicinal plant also may cause serious effects on vital organs and also may cause carcinogenicity for long term uses for treatment of various diseases. Microbial growth including fungus formation also may be responsible for serious adverse reaction of the herbal drugs. To encounter these problems acute and subchronic toxicity can be effectively implemented to evaluate any range of toxicity which may be evolved due to use of the herbal drugs [10,11]. In this review article we will discuss various aspects of serious toxicity of herbal drugs and how to encounter these problems.

Concerns Related to Herbal Drugs

Toxicity

In recent studies it was found that more than 25% of pharmaceutical ingredients contain the chemical which is originated from plant sources (Table 1) [12-15].

Table 1. Toxicological aspect of common herbal drugs used for treatments of various ailments.

Name of herbal drugs	Uses	Toxicity
Aconite	The drug is mainly used for anti-inflammatory and analgesic activity. In addition it is used for Rheumatic arthritis and cardiac disorders	Very fast-acting poison that causes severe side effects such as nausea, vomiting, weakness or inability to move, sweating, breathing problems, heart problems, and death.
Alfalfa	It is very much popular drug used in homeopathic medicine. It contains lots of ion including sodium, potassium, etc.	Auto immune disorder of Systemic Lupus Erythematosus (SLE) like syndrome may be induced in individuals.
Aloe vera	Mainly used as nutritional drink for internal consumption. Minor cuts and bruises can be treated by using Aloe vera ointment or topical formulation	Long term uses may cause depletion of potassium in human body. It may interact with glycoside and may cause life threatening electrolyte imbalance.
Comferey	It is used for treatments of cuts, infection and bruises. Comfrey herbal tea is good for the treatment of knit bones.	The pyroolidine chemicals present in comferey are highly hepatotoxic. This may induce the risk of cancer.
Ephedra	The drug is highly effective for the treatment of respiratory diseases. The drug is also used for obesity treatment and for mood elevation.	
	The ephedra is responsible for serious side effects including restlessness and hypertension. Long term uses of ephedra may damage liver and heart permanently.	
Ginkgo biloba	Mainly used for improvement of mental alertness and memory power.	Long term use can body hemorrhage and reduce platelet activating factor.
Ginseng	It is used for improvement of general immunity. It works as stress remover and antihypertensive agents.	Long term use may cause problem related with blood clotting

To counter all these toxicity effects, proper counseling of the patients with herbal drug physician and experts should be done. Pharmacovigilance of herbal drugs may play an important role to encounter these types of incidents.

Herbal drug interaction

Herbal drugs may interact with conventional drug and may produce some unwanted reaction in human body system. Herbal drug interaction is more dangerous than conventional drug due to presence of enormous pharmacological active constituents in single herbal medicine [16]. Although most of the herbal drugs do not have any problems related to drug interaction, if interaction happens it results in serious consequences. Herbal drug interaction is generally moderate in nature [17]. Due to very narrow therapeutic ranges several lifesaving drugs like ticlopidine, insulin, warfarin, digoxin, and aspirin frequently interact with some herbal drugs [19].

Table 2. List of various herbal drugs interact with conventional drugs.

Name of drug	Uses	Drug interaction
St. John's wort	Hemorrhoids, stomach upset anxiety, insomnia, mild to moderate depression fluid retention	St. John's wort induces clearance of SSRI. Cyclosporine, fluoxetine, digoxin, indinavir, and phenprocoumon, irinotecanand, imatinib type anticancer drug also interact with St. John's wort
Ginkgo biloba	Memory problems, Alzheimer's disease	Exacerbate bleeding in combination with warfarin and aspirin
Salvia miltiorrhiza	Coronary heart diseases, cerebrovascular disorders	Bleeding may be induced in combination with warfarin
Allium sativum	Atherosclerosis and high blood pressure (hypertension)	Plasma concentration may be increased when combined with saquinavir, hypoglycemia may be triggered when chlorpropamide is administered along with Allium sativum
Ephedra	Asthma, bronchitis, hay fever, cold and flu, nasal congestion, cough	Combined with caffeine it may cause life threatening conditions
Black Cohosh	Vaginitis, menopausal disorders ("hot flashes"), uterine spasms and painful menstruation	Black Cohosh may induce hepatotoxicity with the following drugs: atorvastatin, acetaminophen and alcohol
Coenzyme Q10	Natural immune booster	Use with warfarin may cause blood clotting
Cranberry	Supplement of vitamin C	Cranberry may increase effect on anticoagulants
Echinacea	Improve immune system against cold	Echinacea reduce metabolism of caffeine
Ginger	Herbal supplement	Ginger induces interaction with anticoagulants like warfarin, aspirin, or other anticoagulants

Herbal drug researchers are trying to find the exact reasons behind this interaction. Till now the exact reasons for these drug interactions were not fully understood. But some

scientists have investigated that the reason behind interaction between anticancer drugs and herbal medicine is due to activity of metabolic enzyme CYP3A4 and P-glycoprotein [20]. The interaction of various drugs is presented as follows (Table 2).

Allergic reactions

Herbal drugs may interact with conventional drug and may produce allergic reactions. There are many herbal drugs which may produce serious allergic reaction including anaphylactic shock. In addition to anaphylactic shock it may produce itching, pruritus and rashes of skin. Asteraceae family is responsible for various types of serious allergic dermatitis [21-23].

Sunflower is very much familiar to induce contact allergy among florists and gardeners. Aroma oil and various type of volatile oil present in the cosmetics may trigger allergic reaction. The herbal plants belonging to Narcissus family which contains calcium oxalate are highly responsible for serious skin diseases like fissures and dryness, scaling erythematous dermatitis, etc. Existing skin disorders also may be exacerbated due to the contact of calcium oxalate. In addition, the flowers belonging to Asparagaceae family also induced dermatitis skin irritation. Although *Aloe vera* may cause skin irritation due to allergic reaction it is very rare. Garlic (*Allium sativum*), onion (*Allium cepa*) is more frequently used in herbal medicine which also induces skin irritation. Pineapple (*Ananas comosus*) is included in this family. It contains calcium oxalate crystals and bromelain, a proteolytic enzyme whose action is facilitated by the crystals. It is known that pineapple can cause irritations in the mouth (stomatitis, particularly angular cheilitis and perioral dermatitis). Tea tree oil-widely used as a topical disinfectant or camomile can cause allergic reactions.

Table 3. Mutagenicity of various herbal plants.

Name of herbal drugs	Uses	Mutagenic reaction
Anthranoïd such as aloe, cascara, rhubarb and senna.	Used for laxative purpose	Use of anthranoïd laxatives are highly associated colorectal carcinoma
Chaparrel	Used for tea	Cystic renal cell carcinoma may develop after regular uses of Chaparrel tea
Vinca leafs	Used for treatment of various cancerous diseases	Vincristine (VCR), Vinblastine (VBL) and Vinorelbine (VRL) are anticancer agents which may induce genotoxicity

Mutagenic reactions

Herbal drugs may have the potential to change the genetic code of DNA. The common herbal drugs used for the treatment of various ailments have shown some serious mutagenicity [24]. Table 3 depicts toxicity of various plants which shows mutagenicity. Herbal drug interaction is more dangerous compared to conventional drugs due to presence of enormous

pharmacological active constituents in single herbal medicine [25].

Although most of the herbal drugs do not have any problems related to drug interaction, it may result in serious consequences if there's any interaction. Herbal drug interaction is generally moderate in nature [26]. Due to very narrow therapeutic range several lifesaving drugs like ticlopidine, insulin, warfarin, digoxin, and aspirin frequently interact with some herbal drugs [26,27]. Herbal drug researchers are trying to find the exact reasons behind this interaction. Till now it was not fully understood the exact reason for these drug-drug interaction. But some scientists have explored that the reason behind interaction between anticancer drugs and herbal medicine is due to activity of metabolic enzyme CYP3A4 and P-glycoprotein [27]. The interaction of various drug interactions is presented here.

Contamination

One of the biggest problems with herbal drugs is contamination or adulteration. Compared to conventional drugs herbal medicine evaluation of quality control parameter is less stringent. Most of the herbal drugs originated from Asia contain heavy metals like lead, arsenic, mercury, etc. In 1989, a contaminated batch of L-tryptophan herbal drugs was responsible for outbreak of life threatening disease eosinophilia-myalgia syndrome. Another type of contamination is possible in the form of microbial contamination. The improper transportation and humid condition is mainly responsible for fungal infection of herbal drugs. The unscientific method of cultivation and collection of raw herbal drugs also may be one of the salient reasons for pathogenic contamination. Sometimes herbal drugs are contaminated due to exposure of human pathogenic organism [28].

False Authentication

False authentication and identification is a serious issue which may cause fatal consequences for the patients who consume herbal drugs. The false authentication may be due to several reasons, although very of them are may be done deliberately. One of the most common examples of false authentication is ginseng preparation. To identify the difference between false and real drug human expertise is needed to evaluate the morphological structure of the drug. In few cases expert taxonomists are also unable to identify the true herbal drugs. Modern analytical techniques like HPLC, FT-IR and LC-MS can be used successfully to identify the chemical structure of the drugs [29-31]. Yet these techniques are not very accurate and effective to find the adulterant if it is mixed in minute quantity. For this reason it is highly required to find some simple and economic method to evaluate the authentication of the herbal drugs [32-36].

Discussion

In ancient civilization, people used to find the remedies form the natural resources-plants, herbs, as there was no trace of

modern medicines. Even now, among the tribal community, we can find a wide range of natural remedies to treat the health problems or diseases. With the historical experiences which were accumulated over thousands of years, we are now shaping these with a scientific approach. A lot of research and developments are conducted to establish the evidence for the herbal medicines [33-49].

The main issue of a medicine is its effectiveness as well as its safety. Drug toxicity and side effects have recently become a major issue in public health. We can experience the realization gained through the safety monitoring (i.e. pharmacovigilance) in case of modern medicine [34,35]. Herbal drugs although being somehow less toxic and having less serious side effects, it cannot be excluded fully from toxic drugs. Several photochemicals are recently used in pharmaceutical industry for the treatment of various diseases. In addition herbal drugs are also used as nutrient and immune boosters. In previous review and research article many authors have explained in detail various safety issues of herbal drugs. Most of the studies mainly concentrated on side effects of various drugs used as herbal preparation. Very few researchers have pointed out the issue of authentication and contamination [37,38].

The herbal drugs are lacking far behind in proper safety monitoring, adverse event reporting system, etc. Though the regulation and specification of herbal medicines are different country-wise, the need of pharmacovigilance is essential to promote the safe use of herbal medicines. Therefore attempts were made in this review article to address all the challenges of herbal drugs in the recent era in terms of drug toxicity.

Conclusion

Nowadays, herbal medicines and related research are promoted by the government level in many countries like China, India, Nigeria, The United States of America (USA) [39]. For example, Indian government framed AYUSH ministry [40]. The Ministry of AYUSH was formed in 2014 to ensure the optimal development and propagation of AYUSH (Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homeopathy) systems of health care. WHO had already invested in research and development for promising medicinal plants and natural medicines. More and stringent regulatory requirements are apprehended by different regulatory authorities for the safety and efficacy point of view regarding the herbal medicinal products.

Herbal medicine becomes indispensable in modern medicine. The researchers and physicians can hardly afford to deny its utility and therapeutic efficacy. However its unwanted side effects and various health related issues are major concerns in pharmaceutical industry. To overcome this problem, the issue of various side effects of all the drugs should be addressed properly. In this review article we covered all the issues related to unwanted reaction of various photochemical which may contribute a little to the present global health knowledge and understanding.

References

1. Cohen MR. Medication errors. *Nursing* 1998; 28: 11-14.
2. Lee SJ, Horne CH. Herbal products and conventional medicines used by community-residing older women. *J Adv Nurs* 2001; 33: 51-59.
3. Vickers A, Zollman C. ABC of complementary medicine: herbal medicine. *Br Med J* 1999; 319: 1050-1053.
4. WHO. WHO monographs on selected medicinal plants. Geneva, Switzerland WHO 2002a.
5. WHO. Traditional medicine strategy (2002-2005). WHO/EDM/TRM/2002.1. Geneva, Switzerland: WHO 2002b.
6. WHO. WHO guidelines on good agricultural and collection practices (GACP) for medicinal plants. Geneva, Switzerland WHO 2003.
7. WHO. WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems. Geneva, Switzerland WHO 2004.
8. WHO. WHO global atlas of traditional, complementary and alternative medicine. Geneva, Switzerland WHO 2005a.
9. WHO. National policy on traditional medicine and regulation of herbal medicines. Report of a World Health Organization Global Survey. Geneva, Switzerland: WHO 2005b.
10. Alwakeel SS. Microbial and heavy metals contamination of herbal medicines. *Res J Microbiol* 2008; 3: 683-691.
11. Ang HH. Analysis of lead content in herbal preparations in Malaysia. *Hum Exp Toxicol* 2003; 22: 445-451.
12. D'Arcy PF. Adverse reactions and interactions with herbal medicines. Part 1: adverse reactions. *Adverse Drug React Toxicol Rev* 1991; 10: 189-208.
13. D'Arcy PF. Adverse reactions and interactions with herbal medicines. Part 2: drug interactions. *Adverse Drug React Toxicol Rev* 1993; 12: 147-162.
14. Fugh-Berman A, Ernst E. Herb-drug interactions: review and assessment of report reliability. *Br J Clin Pharmacol* 2001; 52: 587-595.
15. Tsai HH, Lin HW, Simon PA, Tsai HY, Mahady GB. Evaluation of documented drug interactions and contraindications associated with herbs and dietary supplements: a systematic literature review. *Int J Clin Pract* 2012; 66: 1056-1078.
16. Na DH, Ji HY, Park EJ, Kim MS, Liu KH, Lee HS. Evaluation of metabolism-mediated herb-drug interactions. *Arc Pharm Res* 2011; 34: 1829-1842.
17. Meijerman I, Beijnen JH, Schellens JHM. Herb-drug interactions in oncology: focus on mechanisms of induction. *Oncologist* 2006; 11: 742-752.
18. Nortier JL, Martinez MC, Schmeiser HH, Arlt VM, Bieler CA, Petein M. Urothelial carcinoma associated with the use of a Chinese herb (*Aristolochia fangchi*). *N Engl J Med* 2000; 342: 1686-1692.
19. Pal SK, Shukla Y. Herbal medicine: current status and the future. *Asian J Cancer Prev* 2003; 4: 281-288.

20. Parle M, Bansal N. Herbal medicines: are they safe? *Nat Prod Rad* 2006; 5: 6-14.
21. Anon. Are your chronically ill patients turning to herbs? *Dis State Manag* 1999; 5: 66-70.
22. Barrett B, Keifer D, Rabago D. Assessing the risks and benefits of herbal medicine: an overview of scientific evidence. *Alt Ther* 1999; 5: 40-49.
23. Beigel Y, Schoenfeld N. A leading question. *N Engl J Med* 1998; 339: 827-830.
24. Bossuyt L, Dooms-Goossens A. Contact sensitivity to nettles and camomile in alternative remedies. *Contact Derm* 1994; 31: 131-132.
25. Fugh-Berman A, Ernst E. Herb-drug interactions: review and assessment of report reliability. *Br J Clin Pharmacol* 2001; 52: 587-595.
26. Na DH, Ji HY, Park EJ, Kim MS, Liu KH, Lee HS. Evaluation of metabolism-mediated herb-drug interactions. *Arc Pharm Res* 2011; 34: 1829-1842.
27. Meijerman I, Beijnen JH, Schellens JHM. Herb-drug interactions in oncology: focus on mechanisms of induction. *Oncologist* 2006; 11: 742-752.
28. Kulkarni CF, Deshpande A, More S. Assessment of microbial contamination in commercial herbal oral medicinal liquids. *Int J Pharm Res Develop* 1999; 2: 191-194.
29. Panusa A, Multari G, Incarnato G, Gagliardi L. High-performance liquid chromatography analysis of anti-inflammatory pharmaceuticals with ultraviolet and electrospray-mass spectrometry detection in suspected counterfeit homeopathic medicinal products. *J Pharm Biomed Anal* 2007; 43: 1221-1227.
30. Puchert T, Lochmann D, Menezes J, Reich G. Near-infrared chemical imaging (NIR-CI) for counterfeit drug identification—a four-stage concept with a novel approach of data processing (Linear Image Signature). *J Pharm Biomed Anal* 2010; 51: 138-145.
31. Lindegardh N, Dondorp A, Singhasivanon P, White N, Day N. Validation and application of a liquid chromatographic-mass spectrometric method for determination of artesunate in pharmaceutical samples. *J Pharm Biomed Anal* 2007; 45: 149-153.
32. Chen SL, Song JY, Hui Y, Shi LC, Luo K, Han JP. Strategy and key technique of identification of Chinese herbal medicine using DNA barcoding. *Chin J Nat Med* 2009; 7: 322-327.
33. Junhua Z, Igho JO, Paul P, Mohamed E. The safety of herbal medicine: from prejudice to evidence. *Evid Bas Compl Alt Med* 2015.
34. Linde K, Jonas WB. Evaluating complementary and alternative medicine: the balance of rigor and relevance. *Essentials of complementary and alternative medicine*. Baltimore Lippincott Williams Wilkins 1999; 57-71.
35. Zhao L, Chan K. Building a bridge for integrating Chinese medicine into conventional healthcare: observations drawn from the development of the Chinese Quality of Life Instrument. *Am J Chin Med* 2005; 33: 897-902.
36. Lv L, Huang W, Yu X, Ren H, Sun R. Comparative research of different *Bupleurum chinense* composition to influence of hepatotoxicity of rats and oxidative damage mechanism. *China J Chinese Mater Medica* 2009; 34: 2364-2368.
37. Ernst E. Herb-drug interactions: potentially important but woefully under-researched. *Eur J Clin Pharmacol* 2000; 56: 523-524.
38. WHO traditional medicine strategy 2002-2005. Geneva: WHO 2002.
39. Bent S. Herbal medicine in the United States: review of efficacy, safety, and regulation: grand rounds at University of California, San Francisco Medical Center. *J Gene Int Med* 2008; 23: 854-859.
40. <http://ayush.gov.in/about-us/about-the-ministry>.
41. Zhu B, Zhang QL, Hua JW, Cheng WL, Qin LP. The traditional uses, phytochemistry, and pharmacology of *Atractylodes macrocephala* Koidz.: a review. *J Ethnopharmacol* 2018; 226: 143-167.
42. Yao CM, Yang XW. Bioactivity-guided isolation of polyacetylenes with inhibitory activity against NO production in LPS-activated RAW264.7 macrophages from the rhizomes of *Atractylodes macrocephala*. *J Ethnopharmacol* 2014; 151: 791-799.
43. Zhang JH, Xin HL, Xu YM, Shen Y, He YQ, Hsien Y, Lin B, Song HT, Juan L, Yang HY, Qin LP, Zhang QY, Du J. *Morinda officinalis* How. A comprehensive review of traditional uses, phytochemistry and pharmacology. *J Ethnopharmacol* 2018; 213: 230-255.
44. Li CQ, He LC, Dong HY, Jin JQ. Screening for the anti-inflammatory activity of fractions and compounds from *Atractylodes macrocephala* koidz. *J Ethnopharmacol* 2007; 114: 212-217.
45. Guo Y, Yin T, Wang X, Zhang F, Pan G, Lv H, Wang X, Owoicho Orgah J, Zhu Y, Wu H. Traditional uses, phytochemistry, pharmacology and toxicology of the genus *Cimicifuga*: a review. *J Ethnopharmacol* 2017; 209: 264-282.
46. Dong H, He L, Huang M, Dong Y. Anti-inflammatory components isolated from *Atractylodes macrocephala* Koidz. *Nat Prod Res* 2008; 22: 1418-1427.
47. Boniface PK, Baptista Ferreira S, Roland Kaiser C. Current state of knowledge on the traditional uses, phytochemistry, and pharmacology of the genus *Hymenaea*. *J Ethnopharmacol* 2017; 206: 193-223.
48. Saleh-E-In MM, Van Staden J. Ethnobotany, phytochemistry and pharmacology of *Arctotis arctotoides* (L.f.) O. Hoffm. a review. *J Ethnopharmacol* 2018; 220: 294-320.
49. Zhang L, Wang Y, Yang D, Zhang C, Zhang N, Li M, Liu Y. *Platycodon grandiflorus*-an ethnopharmacological, phytochemical and pharmacological review. *J Ethnopharmacol* 2015; 164: 147-161.

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