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Original Article

Safety of Medicinal Tropical Natural Products – Concerns and Issues

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ABSTRACT

Background: *No medicinal product is safe whether it is of streamline medicine or belongs to traditional system of medicine. Tropical products of natural drugs, fruits and supplements, no matter how common it's clinical uses, have the potential to cause harm. It is true that adverse reactions are a cost of modern medical therapy, but indigenous drugs used in traditional medicines especially herbs and tropical products are also not safe in true sense. In addition, in recent years, there have been several other high-profile herbal safety concerns that have had an impact on the public health, and there is increasing recognition of the need to develop Pharmacovigilance systems for medicinal herbs and tropical products.*

Methods: *Pharmacovigilance should be a priority for every country with a public health disease. The focused Pharmacovigilance initiatives for the safe treatment of tropical diseases such as malaria, leishmaniasis and schistosomiasis, involving the administration of medicines to large communities are being implemented within the same population with little knowledge of, or regard to, how these various medicines could interact with each other. Moreover, Pharmacovigilance approach to tropical herbal products including natural substances and supplements and monitoring the safety of herbal medicines presents unique challenges.*

Results: *This paper aims to provide a critical overview of the current state of Pharmacovigilance activities for some tropical diseases and herbal tropical medicines at the national and global levels. It will explore in depth the challenges that Pharmacovigilance of herbal medicines presents, consider relevant emerging issues and what steps could be taken to improve the safety monitoring for herbal medicines in the future.*

Conclusion: *Pharmacovigilance practices for herbal medicine are different from that of conventional drugs. The existing systems developed for synthetic medicines and require some modifications to address specific differences of herbal medicines including medicinal products of tropical natural drugs, fruits and supplements. It also needs to be implemented to find and remove secondary toxic metabolites in tropical foods.*

Keywords: *Pharmacovigilance, Tropical products, Unani Medicine, Phytomedicines.*

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INTRODUCTION

The purpose of writing this paper is to study and collect the reports on safety of tropical foods and tropical fruits. We also looked the Pharmacovigilance approach to these substances as direct consequences, interaction with various cytochrome enzymes and substrates and other details of secondary toxic metabolites and processes to make it safe.

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Pharmacovigilance of herbs-based medicine called (Herbovigilance) works towards safety of herbal medication. Adverse reactions are a cost of modern medical therapy, but indigenous herbs-based drugs used in traditional medicines especially tropical products are also not safe. Tropical products of natural drugs and natural supplements, no matter how common it's clinical uses, have the potential to cause harm. Despite, the use of phytotherapy is constantly increasing; consumers and health professionals often ignore important issues like possible interactions between herbs and drugs, adverse effects and simply ineffectiveness of many products. Although, Herbovigilance programme has been geared up in India, but it needs to developed in other tropical countries.

No medicinal product is safe whether it is of streamline medicine or belongs to traditional medicines. Traditional practitioners argue that medicines used and prescribed, do not need any clinical testing as they are being used since ages. They also claim that if the medicines prepared as per traditional formularies, then won't pose any harm. But all medicines are not prepared as per standard format. In this era of competition and also unavailability of unfinished quality raw material, all medicines are not manufactured as per standardization levied by drug regulatory agencies. Any deviation from official pharmacopoeias, may lead to cause adverse reactions. In recent years, there have been several high-profile herbal safety concerns that have had an impact on the public health increasing recognition of the need to develop Pharmacovigilance systems for medicinal herbs and tropical products, known as Herbovigilance.

Pharmacovigilance approach to tropical herbal medicinal products including natural cosmetics, functional foods, aroma (essential oils) and supplements and monitoring the safety of herbal medicines presents unique challenge.

METHODS

To collect and study the evidences of

1. Adverse Drug Reactions caused by Tropical fruits due to Direct Consequence.
2. ADRs caused by certain herbal ingredients.
3. ADRs due to interaction of tropical foods/ fruits with cytochrome enzymes and substrates.
4. Drug interactions of various tropical fruit juices.
5. ADRs due to interaction with P glycoprotein.
6. ADRs of herbs used in cardiovascular system and their notable drug interactions.
7. ADRs due to drugs of two different systems of medicine for same treatment.
8. ADRs due to misidentification of drugs.
9. Secondary toxic metabolites in tropical foods and fruits.

RESULTS

1. Adverse Drug Reactions caused by Tropical fruits due to Direct Consequence:

Various tropical fruits like coconut, passion fruit, papaya, guava, star fruit, pineapple, kiwi, acai, mango and banana and their chemical constituents derived from semi-synthesis, total synthesis and biotransformation and known as bio compounds like alkaloids, naphthaquinone, triterpenoids, furanocoumarins, etc. provide leads to screening for antibacterial, anti-larvicides, anti-estrogen, anti-androgens, etc. These active principles of bio compounds may have direct effect on receptor and enzymes to produce ADRs.

1. Echinacea reported to cause fatigue, dizziness, headache, and gastrointestinal symptoms. Bent hume derma.[1,2,3]
2. Garlic reported to cause nausea, burning sensation in mouth, throat, and stomach, halitosis, and body odor.[1,2,3]
3. Ginkgo biloba reported to cause nausea, dyspepsia, headache and heart palpitations. [1,2,3]
4. Saw palmetto reported to cause headache and diarrhea. [1,2,3]
5. Ginseng reported to cause anorexia, rash, changes in blood pressure and headache. [1,2,3]
6. St John's Wort reported to cause photosensitivity, dry mouth, dizziness, serotonin syndrome and confusion.[4]

2. Few more examples of ADRs caused by certain herbal ingredients:

Potential ADRs	Active ingredient to cause ADR (if Known)	Example of herbs that could be implicated
Allergic		
Hypersensitivity	Sesquiterpene lactones	Arnico, feverfew[5]
Phototoxicity	Furanocoumarins	Celery, wild carrot[5]
Immunity problems	Canavanine	Alfalfa[5]
Cardiac	Cardiac glycosides	Squill[5]
Endocrine		
Hyperthyroid	Iodine	Fucus[5]
Endocrine Disruptors	Triterpenoids	Liquorice[5]
	Isoflavonoids	Alfalfa[5]
	Saponins	Ginseng[5]
	Anti-androgenic agents	Saw palmetto[5]
Irritant		
Gastrointestinal	Pyrrolizidine alkaloids	Comfrey[5]
Renal	Aescin	Horse chestnut[5]
Toxic		
Hepatotoxic	Pyrrolizidine alkaloids	Comfrey[5]
Mitogenic	Proteins	Mistletoe[5]
Convulsant	Volatile oil constituents	Camphor[5]

3. ADRs due to interaction of tropical foods/ fruits with cytochrome enzymes and substrates:

Due to large number of Citrus species and hybrid cultivars, pharmacological studies of these plants are very varied and extensive, only a few pharmacological bioactivities have been reported. Citrus fruit juice–drug interaction may be due to the inhibition of CYP3A by furanocoumarins present in fruits. For example, star fruit is reported as potent inhibitor of Human Cytochrome P450 3A (CYP3A) Activity.[6] However, CYP2C9 cytochrome inhibition by different citrus fruit juices is also investigated. There is only limited information on effect of fruits juice on human CYP 450 (CYP2C9)-mediated drug metabolism activity.

Muneaki Hidaka, et. al. studied nine citrus fruits and eight tropical fruits to see the effect on diclofenac 4'- hydroxylation and tolbutamide hydroxylation by human liver microsomes. In their study, pineapple juice showed potent inhibition of CYP2C9 activity.[7] The addition of (5.0% v/v) of pineapple juice resulted in almost complete inhibition. Bromelain, a cysteine protease in pineapple strongly inhibited CYP2C9 activity. E-64, a cysteine protease inhibitor, almost entirely blocked inhibition by pineapple juice and bromelain. Pineapple juices a potent inhibitor of

CYP2C9, and that the inhibitory effect might be due to bromelain contained in pineapple[7]. In addition to improvement of the human immune system, mangosteen extracts and some xanthones assessed for their interaction with cytochrome P450. Mangosteen consumption should be considered with caution as an adjunct if taken in conjunction with traditional therapeutics since the xanthones showed an inhibitory effect on a number different CYP450.[8]

4. Few more examples of drug interactions of various tropical fruit juices:

1. Orange juice on interaction with alisikiren, atenolol, celiprolol, montelukast, alendronate and clofazimine resulting into the greater decrease in drug bioavailability and potentially lower the efficacy. Orange juice on interaction with fluoroquinolones also causes greater decrease in drug bioavailability, potentially higher risk of therapeutic failure and subsequent bacterial resistance.[9]
2. Apple juice on interaction with fexofenadine, alisikiren and atenolol resulting into the greater decrease in drug bioavailability and potentially lowers the efficacy. [9]
3. Seville orange on interaction with Felodipine resulting into the significant increase in AUC of felodipine and decrease (Y) in the dehydrofelodipine-felodipine AUC ratio (an index of CYP3A4 activity). [9]
4. Pomelo juice on interaction with cyclosporine resulting into the significant increase in AUC and Cmax, and potential higher risk of supratherapeutic concentrations of cyclosporine. Similarly, pomelo juice on interaction with sildenafil resulting into the significantly reduced bioavailability and potential reduced efficacy. [9]
5. Grape juice on interaction with cyclosporine resulting into the significantly decreased (Y) bioavailability and potential higher risk of subtherapeutic concentrations of cyclosporine. Similarly, Grape juice on interaction with phenacetin resulting into the marked reduction (Y) in AUC and Cmax, and a delay in time to peak concentration. [9]
6. Lemon juice on interaction with 99mTc-tetrafosmin resulting into the enhanced hepatobiliary excretion and improved myocardial SPECT image quality. [9]
7. Pomegranate juice on interaction with intravenous iron during hemodialysis causes attenuation in oxidative stress and inflammation induced by intravenous iron. [9]
8. Cranberry juice on interaction with triple therapy medications for H. pylori cause higher eradication rate of H. pylori eradication in females. [9]
9. Blueberry juice on interaction with etanercept causes significantly improved efficacy and reduced side effects of etanercept. [9]
10. Lime juice on interaction with antimalarial (artemether and camoquine) causes improved antimalarial efficacy. [9]
11. Wheat grass juice on interaction with chemotherapy (fluorouracil, adriamycin and cytoxan) resulting into the change in PK/PD effects and significantly reduced (Y) side effects of chemotherapy. [9]
12. Garlic, ginkgo, St John's wort, ginseng, saw palmetto, ginger and cranberry are reported to interact with Anticoagulants, NSAIDs, antiplatelet agents. [10]
13. Garlic, ginkgo, ginseng, cranberry are reported to interact with Hypoglycemic agents. [10]
14. Ginkgo, St John's wort, valerian are reported to interact with Anticonvulsants. [10]
15. St John's wort, ginseng, ginger are reported to interact with Digoxin. [10]
16. Ginkgo, ginseng, kava, cranberry is reported to interact with Diuretics. [10]
17. Garlic, St John's wort, ginseng, cranberry are reported to interact with Antiviral medications for HIV infection. [10]
18. St John's wort, kava is reported to interact with Oral contraceptives. [10]
19. St John's wort, ginseng, kava, cranberry is reported to interact with Chemotherapy. [10]

5. ADRs due to interaction with P glycoprotein:

Achillea milefolium (Asteraceae) inhibits the effects on P-glycoprotein activity[11], Allium sativum (Aliaceae) stimulates the effects on P-glycoprotein activity[12] and Curcuma longa (Zingiberaceae) was found to have no effect on P-glycoprotein activity[13]. This may lead to the change of bioavailability affected by P glycoprotein which increases the risk of experiencing herb–drug interactions.

6. Herbs ADRs could be classified as per WHO System Organ Class (SOC). Following list is an example of SOC - Cardiovascular System with Severe ARs or Notable Drug Interactions:

Herbal Medicine	Adverse Reaction/Drug Interaction	Treatment
Natural cardiac glycosides (>20 plant sources)	Ventricular tachyarrhythmia, bradycardia and heart block	Digoxin-specific Fab antibody
Veratrum (hellebore)	Bradycardia, A-V dissociation, hypotension, and (rarely) seizures	ECG changes responsive to atropine
Crataegus (hawthorn)	Potentiates digitalis activity	NA
***Salvia miltiorrhiza* (dan-shen)**	Potentiates warfarin activity	NA
***Aesculus hippocastanum* (horse chestnut)**	Renal and hepatic toxic effects	Dialysis to reduce toxic levels

7. ADRs due to drugs of two different systems of medicine for same treatment:

A serious adverse drug interaction of two traditional medicines Ruta graveolens Linn (Unani) & Arsenicum Sulfuratum Flavum 1-X (Homeopathy) leading to loss of hair, hyperpigmented patch, dark colored skin and marginal repigmentation around the periphery of the white spot reported in our study.[14]

8. ADRs due to misidentification of drugs:

Euphoria dracunculoides Lam closely resembles Ruta graveolens Linn. Adverse drug reactions like epistaxis, nausea, vomiting and hematuria were reported due to misidentification of Ruta graveolens Linn, when patients consumed it for the treatment of vitiligo. The adverse reactions observed were due to Euphoria dracunculoides and not of Ruta graveolens Linn and caused because of mis-identification.[15]

9. Secondary toxic metabolites in tropical foods and fruits:

Monascus fermented rice (MFR) also known by names angkak, anka, beni koji, and red yeast rice, is the first of MFPs which have been consumed over the Asian countries. MFR is produced by solid state fermentation of rice as substrate with Monascus. The

contemporary method of MFR production includes steaming of rice to semi-gelatinisation state, followed by inoculation with Monascus starter and then incubation in controlled temperature chamber, until the rice grain becomes deep red coloured from inside. It is widely used as food colorant and food supplement in countries as China, Japan, Taiwan, Thailand and the Philippines; because of its therapeutic, flavour, colour and aromatic fragrance. Many scientific studies have reported that MFR is used as a functional food in the management of hyperlipidemia[16], atherosclerosis[17], diabetes[18], osteoporosis[19] and neurological disorder[20]. In addition to improving metabolic syndrome, extracts from MFR also inhibit the proliferation of various cancer cells.[21,22] Its use is increasing in western countries also because of the inclination of consumer towards natural food additives as compared to synthetic ones.

Through traditionally produced MFR is an important designer food preparation with various potential therapeutic properties, there is controversy over its safety due to biosynthesis of secondary metabolite, mycotoxin citrinin. This secondary metabolite is hepatotoxic and nephrotoxic in nature and adversely effects the liver metabolism and kidney function.[23,24] It is biosynthesized through polyketide pathway along with Monacolin K; hence it becomes imperative to reduce citrinin content as per statutory limit i.e. 0.2micrograms/gram for production of MFR as functional food.[25]

The bioactive compound Monacolin K, popularly known as 'Lovastatin', is mainly associated with reduction of blood cholesterol level by inhibition of key enzyme of cholesterol biosynthesis i.e. 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase.[16] Recently, it has also been associated with modulation of insulin sensitivity and signalling in liver and muscle cells of rats.[26]

Monacolin K or lovastatin, a secondary metabolite produced by MFR, has been reported to affect the insulin sensitivity as well as insulin signalling.[26] In the study of Pooja Dutt et al 2019, they found out that among 8 rice varieties studied, Parmal sella came out of best quality with respect to high amylose content, high gelatinization enthalpy, more hardness and low GI. They also produced in solid state fermentation, comparative more monacolin K and low citrinin was biosynthesized in this rice variety with Monascus strains. During reduction of citrinin content, phosphate-ethanol extraction proved to be best with maximum retention of monacolin K and lowering of citrinin level.[27]

DISCUSSION

No medicinal product is safe whether it is of streamline medicine or belongs to traditional system of medicine. Tropical products of natural drugs, fruits and supplements, no matter how common it's clinical uses, have the potential to cause harm. It is true that adverse reactions are a cost of modern medical therapy, but indigenous drugs used in traditional medicines especially herbs and tropical products are also not safe in true sense. These herbal medicines and tropical products of natural drugs and supplements are in fact widely used in health-care in both developed and developing countries. Traditional practitioners argue that medicines used and prescribed by them, do not need any clinical testing as they are being used since ages. They claim that if the medicines are prepared as per traditional formularies, then they won't pose any harm. But in reality, all medicines are not prepared as per standard format. In this era of competition and also unavailability of unfinished quality raw material, all medicines are not manufactured as per standardization levied by drug regulatory agencies. Any deviation from the official pharmacopoeias, may lead to cause adverse reactions. In addition, in recent years, there have been several other high-profile herbal safety concerns that have had an impact on the public health, and there is increasing recognition of the need to develop Pharmacovigilance systems for medicinal herbs and tropical products. Pharmacovigilance should be a priority for every country with a public health disease. The focused Pharmacovigilance initiatives for the safe treatment of tropical diseases such as malaria, leishmaniasis and schistosomiasis, involving the administration of medicines to large communities are being implemented within the same population with little knowledge of, or regard to, how these various medicines could interact with each other. Moreover, Pharmacovigilance approach to tropical herbal products including natural substances and supplements and monitoring the safety of herbal medicines presents unique challenges. This paper provided a critical overview of the current state of Pharmacovigilance activities for some tropical diseases and herbal tropical medicines at the national and global levels. It also explored in depth the challenges that Pharmacovigilance of herbal medicines presents, consider relevant emerging issues and what steps could be taken to improve the safety monitoring for herbal medicines in the future.

CONCLUSION

Ultimate goal of Pharmacovigilance is safe and proper use of effective medicines including of CAM. Pharmacovigilance of Herbal Medicine situation is different from that of conventional drugs. The existing systems developed for synthetic medicines and require some modifications to address specific differences of Herbal Medicines and medicinal products. It also needs to be implemented to find and remove secondary toxic metabolites in tropical foods so there is more way to go.

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