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REVIEW ARTICLE

THE NEED FOR HERBOVIGILANCE

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Abstract

Objective: This communication outlines herbal drug safety, interactions between herbals and modern medicines, and factors that contribute to herb-drug interactions, including pharmacodynamic and pharmacokinetic interactions and their mechanisms.

Methods: The study reviewed the various factors influencing the present pharmacovigilance system in comparison with the herb's related parameters, identified the advantages and disadvantage of the present system and derived modifications which are relevant to herbal drug's safety, efficacy and quality.

Conclusion: The present pharmacovigilance system, being structured dominantlyfor modern medicines, needs to be reoriented to include detailed differences of herbal drugs with the former. Major limiting factors include suboptimal compilation of clinically relevant Herb-Drug interactions (HDIs), scarce reporting from patients and the failure to promptly recognized HDIs by health sector providers. A well-documented HDI-database prepared from appropriate case reports can detect ADR signals effectively.

Introduction: -

Are all herbal drugs safe? The contemporary healthcare paradigm involves concurrent use allopathic remedies with herbals that possibly imitate, amplify, or antagonize each other. Moreover, the expansion of counterfeit herbal drugs poses a significant threat to public health.

Counterfeit herbals and dietary/food supplements are associated[1] with alarming hazards and very serious side effects. Pharmacovigilance of herb-based medicines, also called Herbovigilance or Phytopharmacovigilance, mainly aims to enhance the safety of herbal medications[2]. Herbovigilance addresses two major health risks namely the suboptimal knowledge about herb/drug interactions and data on counterfeit herbal drugs. The former occurs from under-informed physicians / pharmacists and the latter by deliberate deception by addition of spurious or inferior material. [Figure 1].

Many doctors and pharmacists cannot distinguish counterfeit drugs from the original[3].The increasing availability of the internet has facilitated a global communication channel for counterfeiting without political or geographic boundaries.

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Methods: -

Generally speaking, the counterfeit herbal drugs[4] includes different levels of deceptions like adulteration, inferiority, deterioration, admixture, sophistication, substitution etc. 'Substandard drugs', contain less active ingredient than the authentic drug. Fake drug' has no active ingredient. 'Falsified drugs' contain ingredients that are different from the labelled claim. Sophistication involves deliberate addition of synthetic active ingredients in traditional / herbal medicines; such as addition of benzyl benzoate to Balsam of Peru (*Myroxylon balsamumvar. pereirae***)**. The normal shelf life of herbal products is influenced by several factors including storage conditions and stability of active principles. Environmental factors such as light, temperature, humidity, oxidation, presence of pests (like insects, worms, molds and bacteria), etc. contribute to the deterioration of herbal products. [Figure 2] [Figure 3].

Adulteration is an intentional practice by the addition of an entirely different active ingredient in place of an authentic one. Some artificially manufactured materials are used to substitute the original for e.g., artificial invert sugar for honey; yellow coloured paraffin wax substituted for bee's wax, cheap cotton seed oil instead of olive oil etc. Sometimes adulteration practices involve substitution of authentic crude drug with exhausted parts of the same plant from which all the active compounds have been extracted out.

Mistaken identity[5] poses a severe health risk in the selection of the herbs. Many cases of renal toxicity have been linked to the weight loss preparation containing Stephania tetranda, becauseof adulteration with Aristolochia fangchi, containing nephrotoxic aristolochic acid[67]. Star anise (*Illium verum)* a well-known spice used in many cultures is safe, with a long history in herbal medicine and food. However, Japanese star anise, *Illium anisatum* is a close relative with documented potential to cause both neurologic and GI toxicities.

Herbal incense sticks containing volatile synthetic cannabinomimetic compounds pose serious health hazards. Case reports describe psychotic episodes, withdrawal and dependence associated with the use of such incense sticks, similar to syndromes observed with cannabis abuse.

The frenzied use of pesticides during the cultivation of medicinal plants may precipitate these dangerous chemicals in tissues, eventually resulting in teratogenicity or cancer. In February 2006, the World Health Organization[6] launched 'International Medicinal Products Anti-Counterfeiting Taskforce' (IMPACT)[7], responding to the growing public health crisis of counterfeit in herbal drugs. The IMPACT mainly concerns with admixture, inferiority, pesticide residues, deterioration, sophistication, substitution, adulteration, mistaken identity of crude drugs.

ADRs due to Secondary toxic metabolites

Monascus Fermented Rice (MFR) or Red Rice Yeast[9,10], a common, nutritionalsupplement and food colorantin Asia such as Japan, China, Thailand, and Philippines, contains high amounts of the compound called Monacolin-K, associated with reduction of blood cholesterol by inhibition of cholesterol biosynthesis via inhibition of HMG CoA reductase. However, there is controversy over MFR's safety due to the biosynthesis of another secondary metabolite (a mycotoxin) called citrinin during fermentation. Citrinin is hepatotoxic and nephrotoxic. (Citrinin limit :0.2mcg /gram). [Table 1].

Herb/Drug interactions

(HDIs) pose a serious issue of health concern as majority of HDIs are unreported[11,12]. The true prevalence of HDIs is difficult to estimate as the users of traditional, complementary and alternative medicine (TM /CAM) don't disclose this to their physicians for fear of reprimand. Physicians and pharmacists generally lack the knowledge to advise patients on HDIs, because it is sidelined in the Medical /Pharmacy curriculum. See Table 1 and, Table 2 for noteworthy examples of herb/drug or food/drug interactions.

Popular herbal stimulant laxatives such as aloe, rhubarb, and senna, interfere with absorption of almost any intestinally absorbed drugs. Ephedra sinica contains major alkaloids like ephedrine, pseudo ephedrine etc., used as a decongestant and bronchodilator, but also extensively abused as weight loss aids, where prolonged use can lead to hypertension and cardiovascular events.

Drinking tea or coffee can increase gastric acidity, leading to degradation of penicillin and erythromycin[46,47]. Orange juice *(Citrus aurantium*) should not be consumed with aluminium-containng antacids because the juice increases the absorption of aluminum. Orange and citrus fruit juices also decrease the effectiveness of antibiotics[49]. These are good examples of herb-food interactions.

Ginger (*Zingiber officinale*) is a potent inhibitor of thromboxane synthetase and prolongs bleeding time[28]. Therefore, warfarin like drugs interact with ginger, increasing bleeding time. Leafy green vegetables, rich in vitamin E, should not be taken with coumadin because of potential blood clotting[29].

Generally, HDIs occur from Pharmacokinetic interactions (affecting absorption, distribution, metabolism, and excretion of drugs) and Pharmacodynamic interactions[21] such as antagonistic, agonistic and synergistic interactions etc.

Role of P- glycoprotein

P-glycoprotein (P-gP) in the intestine, liver, and kidney plays an important role in the absorption, distribution and excretion of drugs[18]. P-gP not only limits the cellular transport of drugs from intestinal lumen into epithelial cells, but also enhances the excretion of drugs via hepatocytes and renal tubules into adjacent luminal space[13].

P-gP is involved in multidrug resistance by acting as a pump out drugs from cells. St. John's wort [SJW](*Hypericum perforatum*)[14] like herbs induce CYP450 enzymes and P-gP, thereby facilitating the excretion of drugs.

Flax seed (*Linum usitatissimum*), marshmallow (*Althaea officinalis*) and aloes *(Aloe vera*) contain large amounts of mucilage that inhibits the absorption of certain drugs[52]. Licorice (*Glycyrrhiza glabra*) containing herbal preparations may produce corticosteroid like actions due to the presence of glycyrrhizin, a 11-keto steroid similar to corticosteroids. Co-administration of corticosteroids with licorice should be avoided[48].

Combining anticoagulant drugs and anticoagulant herbs, sedative herbs and conventional anesthetic agents can pose life-threatening pharmacodynamic HDIs. It is believed that SJW[14] antagonises MAO and SSRI (selective serotonin reuptake inhibitors), thereby enhancing the drug concentrations to toxic levels. The Cytochrome P450 (CYP) superfamily is generally involved in oxidative, peroxidative and reductive biotransformation of xenobiotics and endogenous compounds, with a high degree of substrate specificity among families. CYP families 1, 2, 3 are principally involved in xenobiotic metabolism while others play a major role in the formation and elimination of endogenous compounds such as hormones, bile acids, and fatty acids. The most important CYP subfamilies[17,22] responsible for drug metabolism in humans are 1A2, 2A6, 2C9, 2D6, 2E1, 3A4, 3A5.

SJW induces CYP1A2 enzyme[14], thereby increasing the metabolism of warfarin and decreasing its anti-coagulant effect. Kava lactones in kava (*Piper methysticum***)** extract inhibit several CYP 450 enzymes, diminishing the elimination of synthetic drugs metabolized through these enzymes, with a corresponding increase both therapeutic actions and adverse drug reactions. Also, co-administration of SJW and cyclosporine after organ transplantation may result in therapeutic failure and graft rejection. SJW-induced enzyme inductioncan antagonize theophylline and protease inhibitors.

Allium sativum (garlic) decreases plasma concentration of saquinavir by CYP 3A4 enzyme induction[26]. Garlic inhibits CYP 2C9, thereby increasing the anti-coagulant action of warfarin. Saw palmetto(Serenoa repens), Kava(*Piper methysticum***)**, and Bromelain induce CYP 2C9, which metabolize the active s-enantiomer of warfarin [27,28] and reduce drug action.GinkgobilobainhibitsCYP 2C9, thereby decreasing the metabolism of celecoxib, glipizide, tolbutamide, piroxicam, tamoxifen etc, enhancing drug action and ADRs[24],but induces CYP 2C19, thereby increasing the metabolism of omeprazole, lansoprazole, warfarin, diazepam, citalopram, amitriptyline etc, leads to the attenuation the drug action.

The major active compounds in tulsi (*Ocimum sanctum*), such as eugenol, carvacrol, and linalool, inhibit CYP1A1&1B1, thereby preventing the conversion of the procarcinogen Benzo [a] pyrene to toxic diolepoxide[15].Benzo[a]pyrene (BAP) is a polycyclic aromatic hydrocarbon (PAH) is an environmental pollutant produced from the incomplete combustion of coal tar, tobacco smoke, automobile exhaust, grilled meat etc.

The toxicity of Benzo[a]pyrene is the result of its bioactivation to toxic diolepoxides by CYP1A1 and CYP1B1enzymes in liver. Diol epoxides are DNA adducts that mutate the p53 tumor suppressor gene, which, in turn leads to cancer[16]. Also, repeated exposure to Benzo [a] pyrene may lead to darkening and thickening of skin, appearance of pimples etc.

Centella asiatica (Brahmi)[53] significantly enhances the oral bioavailability of Amitriptyline. Brahmi non competitively inhibits CYP2C19, CYP2C9, CYP1A2 and competitively inhibits CYP3A4. Ashwagandha (*Withania*

somnifera)[55] induces CYP3A4, thereby attenuating the deleterious effects of ritonavir on blood cells and liver. Ashwagandha with benzodiazepines may result synergistic activity. Coleus forskohli may potentiate anti-platelet medications by inhibiting the CYP2C9 enzyme [51].

Herbs affecting the bioavailability of drugs

Convolvulus pluricaulis (Shankpushpi) decrease bioavailability of phenytoin and piperine present Piper nigrum enhances bioavailability[36] of phenytoin and propranolol by increasing their absorption. The proteolytic enzyme bromelain in pineapple increases the bioavailability of amoxicillin and tetracycline. Ginseng (*Panax ginseng*) increases the risk of hypoglycemia with antidiabetics like tolbutamide, glipizide etc because ginseng itself is reported to possess moderate antidiabetic activity. Echinacea (*Echinacea purpurea*), a known immunostimulant, may decrease the effectiveness of immunosuppressants.

Inhibitors of Organic Anion Transporting Polypeptides (OATPs)

Another concept in HDIs is the evidence for the OATPs in drug absorption[19,20]. Grapefruit juice and orange juice etc., contain flavonoids like naringin and hesperidin, which are effective inhibitors of OATP. The OATP inhibition may reduce systemic exposure to several clinically important medicines. Sweet orange juice seems to reduce bioavailability of ivermectin significantly. Naringin and hesperidin in citrus fruit juices effectively inhibit OATP 1A2 in human trials.

HDI evidences for the clinical risk assessment

Major HDI evidences may be traced to published theoretical proofs, or expert opinion reports on the possibility of HDI in pharmacodynamic[31,32] or pharmacokinetic animal studies, and in vitro studies with limited predictive in vivo value in humans.

Well documented, published case reports with controlled published interaction studies in patients or healthy volunteers by clinically relevant endpoint may give evidences for clinical risk assessment.

Increased vigilance over HDIs[23] among healthcare personals can mitigate instances of health hazard. With more plants being sourced towards therapeutics, the potential for HDI should always be assessed during the non-clinical safety assessment phase in drug development process.

Quality control measures such as checking for therapeutic /analytical marker compounds in bulk herbal products, and mandating voucher specimens, can help alleviate risks of HDIs. Natural products are not automatically safe. When herbal products are co prescribed with OTC drugs, Physician and Pharmacist should investigate the potential of herb-drug interactions[41] [Table 2].

Beneficial Herb-Drug interactions[71]

HDIs are sometimes beneficial[34]. Ginger may prevent drug-induced nausea; capsaicin counters the gastro mucosal damage by aspirin. Hawthorn (*Crataegus oxyacantha*) improves cardiac blood flow due to its coronary vasodilatory effect. Hawthorn flavonoids (quercetin, rutin, apigenin, hyperin, naringenin etc.) are useful to reduce the adverse effects of digoxin in angina treatment. Anti-epileptic drugs can be combined with *Centella asiatica*because of its additive anticonvulsant activity.

Combining *Momordicacharantia*withrosiglitazone reduces its side effects and improves hypoglycemic activity at lower doses[35]. It is reported[37] that garlic reduces the formation of toxic metabolites of paracetamol, and Ginkgo biloba reduces the extra pyramidal side effects of haloperidol.

Rosemary (*Rosmarinus officinalis*) along with doxorubicin and vinblastine improve the chemo preventive effect, by increasing the efflux and intracellular accumulation of the drugs[38]. Antitumor activity of cisplatin is enhanced by silybinin in vitro[39]. Co-administration of Aloe vera liquid preparations with vitamins results in increased bio availability[68]. Aloe vera gel increase the buccal absorption of anti-retro viral drugs like didanosine many folds[69]. β-carotene inhibits P-gP and thereby decreases the metabolism of several anti-cancer drugs in a synergistic fashion [70].

Conclusion: -

The health hazards of HDIs, and counterfeit herbal drugs, can be countered effectively by continuing education programmes for health professionals and social awareness programmes through media, such as television, internet, newspapers etc.

Most patients think that it is not necessary to disclose herbal drug use to physicians who are themselves under-informed on the perils of HDI. Sub optimal reporting on herbal or vegetable materials consumed during conventional drug therapy to doctors and delays in identification of HDI by healthcare providers contribute significantly to major limiting factors for the accumulation of clinically significant HDIs.

A well-documented 'HDI-data-base' compiled from relevant case reports can detect ADR signals effectively[41]. Benefit /Risk analysis can help manage risks and consider measures to prevent adverse events.

Herbovigilance or Phytopharmacovigilance may focus attention on knowledge about HDIs, Herbal drug counterfeit, and ADRs of herbal medicines[42]. The existing Pharmacovigilance systems developed for allopathic medicines should be modified to address specific differences between herbal medicines and modern medicines. Herbal medicines are usually complex mixtures of multiple active principles that require detailed qualitative and quantitative analytical techniques for the precise quality evaluation.

A number of factors influence the plant profile such as parts of the plant used, time of collection, method of collection, diurnal variations, chemotypes and genotypes, harvesting methods, processing of crude drugs, extraction patterns etc[44,45]. Poor reporting by patients and the healthcare providers' inability to recognize HDIs promptly have been identified as major factors limiting the extensive compilation of clinically relevant HDIs. [Figure 2].

Table 1:-Herbal active compounds to cause ADRs[40].

ADRs	Active compound to cause ADR	Herbs associated
TOXIC		
Hepatotoxic	Pyrazolidine alkaloids	Comfrey
Convulsant	Volatile oil compounds	Camphor
ALLERGIC		
Phototoxicity	Furanocoumarins	Celery, wild carrot
Immunity problems	Canavanine	Alfa-alfa
Hypersensitivity	Sesquiterpene lactones	Feverfew
ENDOCRINE DISRUPTORS	Triterpenoids	Licorice
	Saponins	Ginseng
	Isoflavonoides	Alfa-alfa
IRRITANTS		
Gastrointestinal	Pyrazolidine alkaloids	Comfrey
Renal	Aescin	Horse chestnut
ENDOCRINE		
Hyperthyroid	Iodine content	Fucus (edible seaweed)

Table 2: -Beneficial Herb-Drug interactions (BHDIs)[34,35,37,71]

Drugs	ADR with associated symptoms	Herbs useful for BHDI
Aspirin	nausea	Ginger
Aspirin	gastro mucosal damage	Capsicum
Digoxin	Vomiting. Headache, nausea, loss of appetite	Hawthorn
Anti-epileptic drugs	Dizziness, nausea, vomiting, fatigue, vertigo, ataxia, blurred vision	additive anticonvulsant activity of*Centella asiatica* and reduce side effects of anti-epileptic drugs.
Rosiglitazone	Chest pain or discomfort, increased hunger and urination	*Momordicacharantia*
Paracetamol	Toxic metabolites	Garlic
Haloperidol	extra pyramidal side effects	*Ginkgo biloba*
Anti-cancer drugs	the dose of drugs can be reduced and thereby side effects if taken along with β-carotene	β-carotene containing herbs and vegetables

Table 3: Herb /Drug interactions

Herbs	Causative factors of HDI	Results of interaction with conventional drugs
St. John's wort[14] (*Hypericum perforatum*)	Induces CYP1A2 and thereby increase the metabolism of drugs CYP3A4 induction, P-gP induction	Warfarin and its anti-coagulant action will be reduced Protease inhibitors and their action will be reduced cyclosporine co-administration after organ transplantation may result in cyclosporine therapeutic failure in transplant graft rejection Atorvastatin action will be reduced
Garlic (Allium sativum)[26]	Induce CYP 3A4 and thereby decrease the metabolism of drugs Inhibits CYP 2C9, Inhibit P-gP	Decrease the metabolism of Saquinavir, which may results in adverse drug reactions. Increase the anti-coagulant action of Warfarin, which may result in increased bleeding Reduce docetaxel clearance
Ginger (Zingiber officinalis)[28]	Inhibits thromboxane synthetase thus, prolongs bleeding time.	Warfarin like drugs interact with ginger and result in excess bleeding and extends the time of bleeding
Leafy green vegetables,[30,33] almonds and walnuts	Vegetables and nuts rich in vitamin K[30] could counteract the effects of drugs.	Should not be taken along with Warfarin or heparin like anti-clotting drugs may result in blood clotting.
Wheat germ oil, almonds, pumpkin, peanuts, peanut butter, soya bean oil	Rich in vitamin E [29,33]	vitamin E rich foods should be avoided along with anti-clotting agents like warfarin as these foods will also enhance the anti-clotting process with the drug and result in increased bleeding.
Tea, coffee[46,47]	Increase the acidity of stomach	Actions of penicillin and erythromycin will be reduced with the consumption of tea or coffee as these herbal agents will increase the acidity of stomach and result in degradation of the antibiotics
Grapefruit juice[25]	Constituents of grape fruit juice inhibit the enzymes (CYP1A2, CYP3A4, CYP2C9), that metabolize the drugs which leads to enhanced levels of drugs in the blood, and finally cause severe toxicity.	Results in increased blood levels of Saquinavir, Acyclovir, Lovastatin, Atorvastatin, Nifedipine, Amiodarone, Clomipramine, Carbamazepine.
Liquorice (*Glycyrrhiza glabra*)[48]	CYP 2C9, 3A4 induction Glycyrrhizin present in liquorice is 11-keto steroid, which will act like cortico steroids or it will aggravate the cortoco steroid actions	Warfarin, lidocaine actions will be reduced The action of cortico steroids will be enhanced due to synergistic action Increases effects of spironolactone
Naringin and hesperidin in citrus fruit juices[49]	Inhibits Organic Anion Transporting Polypeptides (OATP) 1A2	Reduce the bioavailability of ivermectin
Kava (*Piper methysticum*)[27,28] Bromelain (pineapple) Saw palmetto	induce CYP2C9	Anti-coagulant drug warfarin's action will be reduced.
Ginkgo biloba [24]	inhibits the liver enzyme CYP2C9	decrease the metabolism of the drugs like celecoxib, glipizide, tolbutamide, piroxicam, tamoxifen
Coleus forskohli[50,51]	inhibit the CYP2C9	potentiate the effects of anti-platelet medications.
Pepper (*Piper nigram*)[36]	increasing the absorption.	enhance bioavailability of phenytoin and propranolol
Flax seeds, Marshmallow and Aloes[52]	inhibits the absorption of certain drugs	Due to the presence of large amounts of mucilage in these herbs, which inhibit the absorption of drugs
Centella asiatica (Brahmi)[53]	non competitively inhibits CYP2C19, CYP2C9, CYP1A2 and competitively inhibits CYP3A4	Enhances the oral bioavailability of Amitriptyline. Brahmi taken together with drugs for Alzheimer's disease e.g.: Donepezil may increase the side effects of the drug. Brahmi together with thyroid hormone pills may increase the side effects of thyroid hormones in the body due to its synergistic activity.

Ocimum sanctum (Tulsi)[15,16]	The major active compounds in tulsi, like eugenol, carvacrol, and linalool inhibit CYP1A1&1B1 and prevent the conversion of the procarcinogen Benzo [a] pyrene to toxic diolepoxide.	The toxicity of Benzo[a]pyrene is the result of its bioactivation to toxic diolepoxides by CYP 1A1 and CYP1B1enzymes in liver. Repeated exposure of Benzo [a] pyrene may lead to darkening and thickening of skin, appearance of pimples etc.
Amla (*Phyllanthus emblica*)[54]	Amla contains rich amounts of tannins which react with iron. The ascorbic acid present in Amla degrades at high temperature; therefore, raw amla powder is suggested instead of processed powder. Amla contains high levels Calcium;	lower the iron levels in the blood and decrease the effect of iron tonics. Raw powder is suggested in order to avoid degradation of ascorbic acid. Too much intake of amla may be avoided to reduce the risk of kidney stones.
Ashwagandha (*Withania somnifera*)[55]	Aswagandha induces the CYP3A4 Synergistic activity with drugs	while administering along with ritonavir, ashwagandha protects the blood cells and liver from the deleterious effects caused by the drugs. Aswagandha with benzodiazepines may result in synergistic activity with sedative drugs like clonazepam, diazepam, lorazepam, etc.
Acorus calamus,[56] tomato (melatonin) and pomegranate	Additive effects	Anti-epileptic effects of carbamazepine can be enhanced, if taken together with these herbs.
Echinacea angustifolia [57] *Echinacea purpure*	Antagonistic action	The immunostimulant actions of Echinacea may decrease the effectiveness of immunosuppressant drugs.
Valeriana officinalis[58], V. wallichi	Synergistic action	May potentiate the effects of CNS depressants
Noni fruit (Morinda citrifolia), alfalfa (Medicago sativa), Dandelion (Taraxacum officinale),	contain very high potassium levels[59,64] Hyperkalemic, hepatotoxic	corticosteroids or diuretics hypokalaemia actions may be countered
Soy milk	Improve clotting process	Decreases effectiveness of warfarin
Passion flower (Passiflora incarnata)[60]	Additive effects	Enhance CNS depressants drugs effect
Piper longum L.[61]	Inhibition of CYP3A4, CYP2D6 and CYP1A2	Actions of drugs like Verapamil, digoxin, propranolol are decreased.
Curcuma longa L.[61]	Inhibition of CYP3A4, CYP1A2, CYP2B6, CYP2C19, CYP2C9	Losartan, rosuvastatin, warfarin, clopidogrel actions will be reduced
Zingiber officinale[61]	CYP2C9 (potent inhibition), CYP3A4 (moderate inhibition)	Decrease the effect of Nifedipine, Phenprocoumon
Terminalia bellirica[61]	Inhibition of CYP3A4, CYP2D6	Decrease the effect of Diltiazem
Terminalia arjuna[62]	Synergistic effect	with anti-hypertensive drugs
Salvia miltiorrhiza[61]	Inhibition of CYP1A2, CYP2C9, CYP2C6, CYP2C11	Warfarin effect will be enhanced
Panax ginseng[61]	CYP3A4 (inhibition)	Nifedipine effect will be enhanced
Mentha piperita L.[63]	CYP3A4 (inhibition)	Felodipine effect will be enhanced
Silybum marianum (milk thistle)[63]	CYP2C9 inhibition	Losartan effect will be enhanced
Schisandra chinensis Magnolia berry or five-flavour-fruit[65]	P-gP inhibition	Talinolol effect will be reduced
Aloe vera[66]	Risk of hypokalemia	when taken along with corticosteroids or diuretics
β-carotene[71]	P-gP inhibition	decrease the metabolism of several anti-cancer drugs, results in enhanced action, and also can reduce the drug dose.

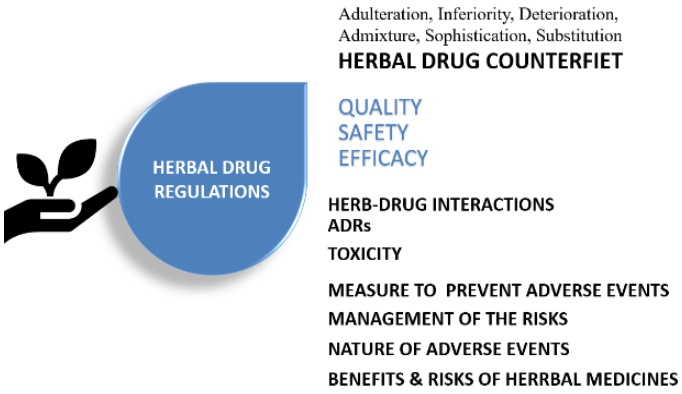

Figure 1: - Safety monitoring of herbal medicines in pharmacovigilance systems.

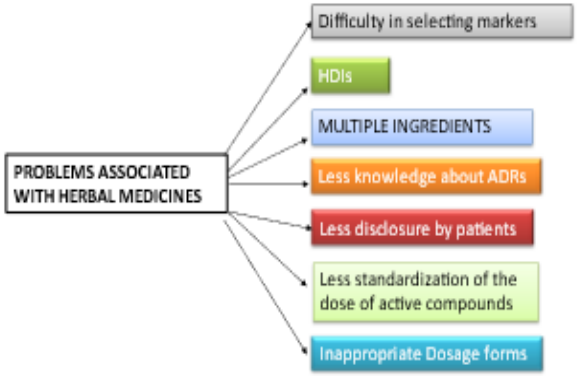

Figure 2: - Problems associated with herbal medicines.

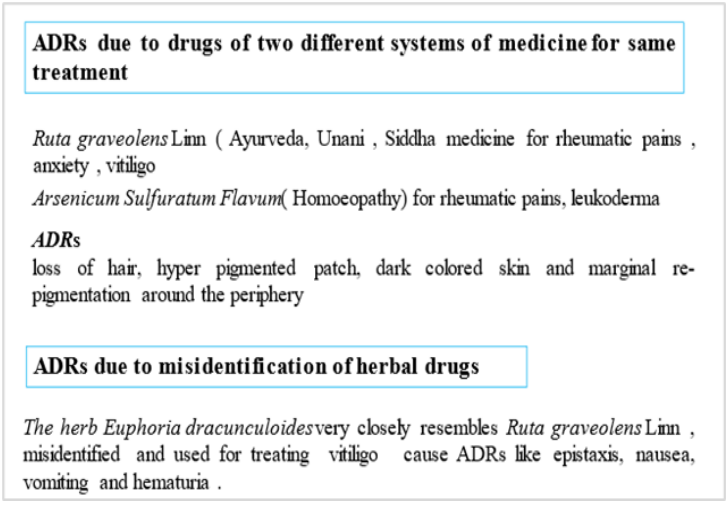

Figure 3: ADRs due to drugs of two different systems of medicine for same treatment /ADRs due to misidentification of herbal drugs[8]

Conflict-of-Interest: Nil.

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