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Review Article

Antihypertensive Drugs Interaction with Herbal Medicine – Review

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Abstract

The purpose of this review is to focus on the interaction that have been reported between antihypertensive drugs and herbal medicine. Herbal medicines are used for the bulk of treatments, particularly by older people that conjointly consume antihypertensive medication. Antihypertensives are categorized into five most commonly used classes such as beta-blocker, diuretic, calcium-channel blocker, angiotensin converting-enzyme (ACE) inhibitor and Angiotensin-II receptor blocker. Herbal medicines may mimic, magnify, or oppose the impact of anti-hypertensive drugs. Overall, the published data are sparse and comprise of both pharmacokinetic and pharmacodynamic interaction. Pharmacokinetic interactions include *Garlic, Ginkgo, Roselle, Guggul, Piperine, Capsicum, St john wort* and *Grapefruit juce* that may alter the bioavailability, Cmax, tmax, AUC of antihypertensive drugs by induction or inhibition of CYP 3A4 metabolizing enzyme. Pharmacodynamic interaction between Spirnolactone with *Liquorice* shows antagonistic effect and Captopril with *Garlic* shows synergistic effect. So, there is atmost need to caution patients against mixing herbs and pharmaceutical drugs.

1. INTRODUCTION

In recent years, herbal medicines in most developing countries have been used to treat a wide range of conditions[1] for the maintenance of good health, providing an idea about new areas of research[2]. India is distinguished as a global biodiversity hotspot where ecology and evolutionary factors favoured huge species diversity with over 1740 medicinal and aromatic plants with various traditional and modern medicinal uses[3].Various herbs and herbal medicine had been used with apparent safety in traditional societies for many centuries, when they are combined with pharmacological agent and may cause a potential interaction between them. Reports show that about 15–20% of individuals on prescription medications also use herbal supplements and less than 40% of patients disclose to their physicians the usage of herbal remedies, although they feel severe side effects—because of the fear of censure or rebuke. The problem that many physicians are themselves not always familiar with the potential for herb–drug interactions. Hence, it promotes credible research on the safety and efficacy of combined herb–drug treatment[4].

Hypertension is the most common cardiovascular disease. It is defined as a sustained increase in blood pressure ≥140/90 mm Hg, which is a principal cause of stroke and major contributor to coronary artery disease, cardiac failure, renal insufficiency and dissecting aortic aneurysm. Antihypertensive drugs lower blood pressure by actions on peripheral resistance, cardiac output, or both[5]. There are nine different antihypertensive drug classes. Diuretics, *β*-blockers, ACE inhibitors, angiotensin II receptor blockers, and calcium channel blockers are considered primary antihypertensive agents. These agents are used to treat most of hypertensive patients[6]. Few (and poorly documented) cases of herbal interactions like *Ginkgo, Liquorice, Golden root , Grapefruit juce, Garlic, St John's wort* and *Guggul* etc with antihypertensive drugs by different mechanism have been reported[7].

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The issue of herb-drug interactions may have been responsible for severe consequences. The nature of herb-drug interactions is not necessarily a chemical interaction between a drug and a herb component to produce a toxic reaction. Instead, the interaction may involve having a herb component cause either an increase or decrease in the amount of drug in the blood stream[8] So, the aim of this review is to provide a critical overview of the existing data on interactions[9] of herbs and antihypertensive drugs which are based on in vitro experiments, animal studies, speculative and empirical evidence[7].

2. MECHANISM OF HERB-DRUG INTERACTION

A "possible interaction" refers to the possibility that one substance may alter the bioavailability, or the clinical effectiveness of another substance, when two or more substances are given concurrently. Most of the possible interactions may be classified in two major categories: pharmacokinetic and pharma-codynamic interactions[10].

2.1 Pharmacokinetic Interaction

Pharmacokinetic interactions occur when herbs changes the absorption, distribution, metabolism, protein binding, or excretion of a drug that results in altered levels of the drug or its metabolites[11]. Absorption is a complex multifactorial phase in pharmacokinetics, and one of the determinants of the clinical outcomes of drug therapy[12]. Drug absorption involves many phases, to optimise the pharmacological effects and minimise the toxicological activity of oral drugs. The mechanisms of action of these systems are based on the physiological gastrointestinal characteristics of pH and motility[13]. Interactions with these could affect the mechanisms of drug release and the solubility of ionisable drugs.

Interactions affecting drug absorption may involve the active transporters located in the intestinal membrane. Absorption in the apical/brush-border or serosal/basolateral localisations of enterocytes is mediated by influx carrier proteins such as ASBT, OATPs, ENT1,2, SGLT1, MCT1, CNT1,2, OCTN2 and PepT-1. These proteins are involved in the transport of many physiological compounds, including peptides, organic anions and cations, amino acids, nucleosides, as well as a large variety of drugs such as beta-lactam antibiotics, ACE inhibitors, biphosphonates, methotrexate, etc. Efflux transporters mediate the expulsion of xenobiotics from

enterocytes to the lumen in order to avoid absorption in systemic circulation, playing an important role in detoxification. Some of these transporters are the ATP-binding cassette (ABC) family protein P-glycoprotein (P-gp or MDR-1) , multidrug resistance associate protein 2 (MRP-2 or ABCC2), and breast cancer resistance protein (BCRP or ABCG2), all of which are expressed on the apical membrane of human and rodent intestine and elsewhere[12].P-glycoprotein (P-gp) is a member of the ABCB (MDR/TAP) subfamily. During drug transport, the development of highly selective P-gp inhibitors is an attractive goal to reduce potential toxicity[14].

Cytochrome P-450 (CYP) superfamily enzymes such as CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 are responsible for oxidative metabolism of drugs(10,12). CYP3A4 is a major contributor to the presystemic metabolism of drugs administered orally. Because CYP3A4 has an extremely wide substrate specificity and many *in vitro* and *in vivo* interactions involving bioactive compounds, it appears to mediate the oxidation of approximately 40-50% of the drugs administered to humans[15]. A herbal constituent can also be an inducer or inhibitor of one or several CYP isoenzyme or efflux systems[16]. If herbs induce one or several CYP isoenzyme or efflux systems, then higher the metabolism, higher efflux and lowering the plasma concentration of drug will occur. This will reduce the drug action or vice-versa. For e.g., St John's wort is a known inducer of the cytochrome P450 isoenzyme CYP3A4 by which ciclosporin is metabolised. Concurrent use of st john,s wort reduces ciclosporin levels. It has also been suggested that St John's wort affects ciclosporin reabsorption by inducing the drug transporter protein, P-glycoprotein, in the intestine[17].

Most drugs and herbs do not appear to have any clinically significant interactions affecting distribution, and can be safely taken together. Interactions occur during the distribution phase if the drug has a narrow range of safety index and is highly protein-bound[10]. For example, warfarin (Coumadin) is very sensitive to changes in distribution because it has a high affinity to protein and a very narrow therapeutic range[18].

One more possible mechanism for producing herbal-drug interactions is modifying in renal clearance of a drug. Herbals that can inhibits tubular uptake or in other ways that can interferes with the renal clearance of a drug should be considered as having potential to produce pharmacokinetic herbal-drug interactions[19].

2.2 Pharmacodynamic Interaction

Pharmacodynamic interaction are related to the pharmacologic activity of the interacting agents and can affect organ systems, receptor sites, or enzymes[20].A herb can potentially mimic, increase, or reduce the effects of co-administered drugs through simultaneous effects on the same drug targets. If the effect of the drug in combination with the herbal medicine is enhanced (e.g., Synergistic or additive effect), unfavourable on-target toxicity may occur. By contrast, some herbal remedies may contain compounds with antagonistic properties, which are likely to reduce drug efficacy and produce therapeutic failure[21].for e.g., Hypnotic activity of benzodiazepines is increased by valerian and the anticoagulant action of warfarin is enhanced by ginkgo and possibly by many other herbs[22]. An example of an antagonistic interaction is when herbal with high caffeine content, such as *Guarana (Paullinia cupana)*, is administered with a sedative-hypnotic may antagonized their effect[19].

3. HERBAL INTERACTION WITH ANTIHYPERTENSIVE DRUG

3.1 Diuretics

Diuretics shows their effect on hypertension treatment by promoting the expulsion of urine (measured as the urine volume [UV] excreted) and urinary sodium from the body and this helps reduce the volume of blood circulating through the cardiovascular system[23]. Thiazide and thiazide-like diuretics are widely used in the treatment of hypertension[24].

Ginkgo is a peripheral vasodilator[25], is used for the treatment of a variety of conditions today, which include asthma, bronchitis, tinnitus, Alzheimer's disease and other dementias, decreased memory, sexual dysfunction and multiplesclerosis[26]. Surprisingly, an elderly patient was found to have a further increase in blood pressure after taking *Ginkgo* while receiving a thiazide diuretic (not specified in the original paper) for hypertension[27,30].

Garlic is one of the best selling herbal remedies today and is also used as a food or spice. This herb contains numerous volatile sulfur compounds such as alliin, allicin, diallyl disulfide, ajoene etc, having antibacterial, antiviral, antifungal, antihypertensive, blood glucose lowering, antithrombotic, antimutagenic and antiplatelet actions. Like most other herbal drugs, *Garlic* is found to interact[26] with hydroclorthiazides. It will increase the bioavailability and half-life of hydrochlorthiazide along with decrease in the clearance and elimination rate constant[28].

Liquorice may offset spironolactone's effects. *Liquorice* is advocated as an antispasmodic and anti-inflammatory herb for use in gastritis and peptic ulcer disease. Due to the potassium excretion mechanism of liquorice, spironolactone's antihypertensive effects may be diminished by liquorice. Hence liquorice shows antagonistic effect with spirnolactone[29]. The *liquorice* with some other antihypertensives may produce additive effect due to potassium excretion as both[30].

Roselle are used for the preparation of homemade refreshing drinks and are also used medicinally Particularly diuretic and antihypertensive potentials. Co-administration of *Roselle* with hydrochlorthiazide caused a significant increase in the volume of urine excreted and resulted in a decrease in the pH of urine and the concentrations of sodium, bicarbonate, and chloride ions and prolonged the plasma concentration, the mean area under the concentration-time curve, and the volume of distribution of hydrochlorthaizide[31].

3.2 β-Blockers

Beta-blockers are used as first-line therapy for hypertension because they have long-term favourable effects on all-cause and cardiovascular mortality[32]. Antagonism of adrenergic receptors affects the regulation of the circulation through several mechanisms, including a reduction in myocardial contractility, heart rate, and cardiac output. Blockade of the beta receptors of the juxtaglomerular complex, reducing renin secretion and thereby diminishing production of circulating angiotensin II. This action likely contributes to the antihypertensive action of this class of drugs. Adrenergic receptor antagonists may lower blood pressure by other mechanisms, including alteration of the control of the sympathetic nervous system at the level of the CNS, altered baroreceptor sensitivity, altered peripheral adrenergic neuron function, and increased prostacyclin biosynthesis[5].

The effect of *Piperine* on the bioavailability and pharmacokinetics of propranolol has been examined in a crossover study. Propanolol in combination with piperine significantly enhanced the systemic availability and area under curve (AUC) of propanolol[33].

Guggul is obtained from the bark of the Guggul tree[34]. Guggulipid, an active constituent of *Guggul* significantly reduced peak plasma concentration (Cmax) and (AUC) of propanolol in normal volunteers. Such interaction in patients receiving propanolol with Gugulipid may lead to diminished efficacy or nonresponsiveness due to significant reduction in bioavailability[35]. These interactions may be due to activation of pregnane X receptor by Guggulsterone, which leads to upregulation of the enzymes responsible for biotransformation of propranolol. It has been shown in rats that administration of Guggulsterone significantly increased expression of cytochrome P450 genes, which are responsible for metabolizing most drugs[34].

Combination therapy of *Garlic homogenate* with propanolol cause increase in the bioavailability and half life along with decrease clearance and elimination rate constant of propanolol it is found to be most effective in reducing systolic blood pressure[36].

3.3 ACE Inhibitors

Patients with hypertension and ischemic heart diseases are candidates for treatment with ACE inhibitors because administration of ACE inhibitors in the immediate post-myocardial infarction period has been shown to improve ventricular function and reduce morbidity and mortality.Captopril is an angiotensin-converting enzyme inhibitor that is used in the treatment of hypertension and congestive heart failure. Concurrent administration of captopril with fresh *Garlic homogenate* or its bioactive constituent, *S-allyl cysteine* produces synergistic antihypertensive and cardioprotective effects[37].

The therapeutic inhibition of angiotensin converting enzyme (ACE) is associated with the production of a dry cough. The exacerbation of artificially induced cough by ACE inhibition may be the result of a

local increase in perineuronal substance P or bradykinin concentrations within the lung[38]. So, *Capsicum* when taken with ACE inhibitors may cause the risk of cough[39].

3.4 Angiotensin-II Receptor Blockers

The importance of angiotensin II in regulating cardiovascular function has led to the development of nonpeptide antagonists of the AT_1 angiotensin II receptor for clinical use. Losartan, Candesartan, Irbesartan, Valsartan, Telmisartan and Eprosartan have been approved for the treatment of hypertension[5].Administration of the herbal medicinal product of *Rhodiola rosea* with Losartan significant increase the maximum plasma concentration (C(max)), the area under the curve (AUC) and the apparent total body clearance (CL/F) of losartan in rabbits which are substrates of both CYPs and P-gp[40].

3.5 Calcium Channel Blockers

Calcium channel blockers (CCBs) are diverse group of drugs used to manage many different cardiovascular diseases. CCBs have been widely prescribed for the treatment of hypertension, angina, and supraventricular arrhythmias because of their efficacy and a low incidence of adverse effects[41]. There are three types of calcium channel blockers (CCBs) in common use, of three distinct chemical classes: phenylalkylamines (e.g., Verapamil), benzothiazepines (e.g., Diltiazem), dihydropyridines (e.g., Amlodipine,felodipine, Nicardipine, Nifedipine, Nimodipine)[42].

Ginkgo is often used by elderly persons because of its ability to improve cognitive function in persons with Alzheimer's disease and dementia and to improve blood flow in persons with peripheral vascular disease, tinnitus, or memory impairment[43]. It is confirmed that the oral coadministration of *Ginkgo* and Diltiazem(DTZ) to rats increased the bioavailability of DTZ by inhibiting both intestinal and hepatic metabolism, at least in part, by a mechanism-based inhibition for CYP3A4[44]. It also reduce the metabolism of nifedipine, a CYP3A4 substrate, and increase its levels[17].

Grapefruit juice inhibits intestinal CYP3A4, and only slightly affects hepatic CYP3A4. This is demonstrated by the fact that intravenous preparations of drugs that are metabolised by CYP3A4 are not much affected, as compared to the oral preparations of the same drugs. These interactions result in increased drug levels. *Grapefruit juice* has little effect on hepatic CYP3A4 and this is borne out by the fact that it interacts with oral but not intravenous preparations. Therefore, the sensitivity of the interaction with *Grapefruit juice* may be related to the oral bioavailability of the calcium- channel blocker. Thus, Amlodipine and Diltiazem with high bioavailability are least affected, Nifedipine is intermediate; and felodipine and Nisoldipine, which have lower bioavailability, are most sensitive to the activity of *Grapefruit juice*[17].

St. John's wort, a commonly used herbal antidepressant, has been shown to induce CYP3A4 and P-glycoprotein and thus alter the pharmacokinetics of various drugs. Nifedipine, prototype of the dihydropyridine class of calcium channel blockers, is widely used in the treatment of hypertension. Coadministration of *St john's wort* with Nifedipine may increase the metabolism of Nifedipin by inducing the metabolizing enzyme CYP3A4[45].

Verapamil reduces arterial pressure by inhibiting calcium ion influx into the vascular smooth muscle cells, which results in a decrease in smooth muscle tone and vascular resistance[7]. Repeated administration of *St John's wort* with verapamil significantly decreased the bioavailability of R- and S-verapamil. This effect is caused by induction of first-pass CYP3A4 metabolism, most likely in the gut, because the jejunal permeability and the terminal half-life were unchanged for both enantiomers[46]. Table-1 reports the herbal remedies involved in interaction with antihypertensive drugs.

Table 1: Reported interaction between Antihypertensive drugs and herb

Antihypertensive class	Drug	Interacting herb	Interaction outcomes	Reference
Diuretic	Thiazides	*Ginkgo biloba* (Ginkgo)	↑ Blood pressure	27
		Allium Sativum (Garlic)	↑ Bioavailability and half-life of hydrochlorthiazide along with ↓ clearance and elimination rate	28
		Hibiscus sabdariffa (Roselle)	↑ Volume of urine excrete, ↓ pH of urine and the conc. of sodium, bicarbonate, and chloride ions and prolonged the Cmax, AUC, Vd of hydrochlorthaizide	31
	Spirnolactone	*Glycyrrhiza glabra* (Liquorice)	Antagonistic effect	29
	Antihypertensive drugs		Additive effect	30
Beta blockers	Propanolol	*Piper nigrum* (Black Piper)	↑ t max, Cmax, AUC by CYP 1A2 inhibition	33
		Commiphora mukul (Guggul)	↓ AUC, Cmax and reduced bioavailability	34
		Allium Sativum (Garlic)	↑ Bioavailability and half-life along with ↓ clearance and elimination rate constant	36
ACE inhibitor	Captopril	*Allium Sativum* (Garlic)	Produces synergistic antihypertensive effect	37
	ACE inhibitor	*Capsicum annum* (Capsicum)	Cause risk of cough	39
Angiotensin-II receptor blocker	Losartan	*Rhodiola rosea* (Golden root)	↑ Cmax, AUC and CL	40
Calcium channel blocker	Diltiazam	*Ginkgo biloba* (Ginkgo)	↑ Bioavailability of drug by inhibiting CYP3A4	44
	Felodipine	*Citrus paradisi* (Grape fruit juce)	↑ Bioavailability of Felodipine	17
	Nifedipine	*Hypericum perforatum* (St Jhon's wort)	↓ Cmax , AUC by Induction of CYP3A4	45
		Ginkgo biloba (Ginkgo)	↓ Metabolism of Nifedipine by inhibiting CYP3A4 isoenzyme, ↑ Cmax .	17
	Verapamil	*Hypericum perforatum* (St John's wort)	↓ Bioavailability of verapamil by Induction of intestinal CYP3A4	46

AUC: Area under curve, C_{max}: Maximum plasma concentration, Vd: Volume of distribution, CL: Clearance, t_{max}: Maximum time

4. RISK ASSESSMENT OF HERB–DRUG INTERACTIONS

The concomitant use of conventional and herbal medicines can lead to clinically relevant herb–drug interactions[47].The process of clinical risk assessment helps reduce the untoward consequences of these interactions. This is generally divided into three phases: risk identification, risk reduction or elimination, and a final evaluation of the adopted risk reduction strategies[12]. First phase of clinical risk management requires that hazards are identified and stratified in terms of evidence, probability and significance. It is important to distinguish the following parameters when stratifying the clinical risks of herb–drug interactions: (i) quality of the evidence for the interaction; (ii) seriousness of the resulting adverse reaction; (iii) incidence of the adverse reaction; and (iv) existence of risk factors resulting in increased seriousness or increased incidence of the adverse reaction[48] For full risk identification, it has been considered the severity and incidence of adverse reactions, as well as the presence of risk factors relating to the user or product that could aggravate them[12]. Second phase of clinical risk management aims to reduce health risks, at the identification of resources, and at the execution of selected strategies[47]. Pharmacist can play a vital role for risk reduction by appropriately dispensing medicine and taking due care of patient's history and medication profile[43]. The third phase in clinical risk management is the evaluation of risk minimization strategies, i.e., which works

effectively and efficiently. This final phase is crucial in the clinical risk management of drug–drug interactions, therefore should not be overlooked in the risk management of herb–drug interactions[47].

5. CONCLUSION

The concomitant use of herbal medicines and pharmacotherapy is spreading widely. Hence, it becomes mandatory to explore the possible interactions of these drugs with present day therapeutic agents. Such an approach would help to reduce the risk of any potential interaction as well as help in providing adequate therapeutic benefits to the end uses. Here, we have reviewed the literature to determine the possible interactions between herbal medicine and antihypertensive drugs. These interactions show that herbal medicine may alter the bioavailability and pharmacokinetic parameter of drugs. Pharmacodynamic interactions may produce synergestic or antagonistic effect. Thus, it is necessary to consider herbal medicines as regular medicines and explore the possibility of interaction with concomitantly administered drugs. The interaction with herb may be beneficial, harmful or may reduced the effect of prescribed drug.

Hence, combine use of herbal with antihypertensive medications should only be done after consultation with a physician. Preliminary research data on combination of herbals and drugs is to be provided to educate pharmacists and physicians for safe and efficacious use of drug and encourage further clinical research**.**

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