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A COMPREHENSIVE REVIEW ON THE COMBINATION THERAPY OF SYNTHETIC ANTIHYPERTENSIVE DRUGS WITH NATURAL BIOACTIVES

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Abstract

This review aims to examine the interactions between antihypertensive drugs and herbal medicine. Herbal medicine is widely utilized for treatment, especially among older individuals who also take antihypertensive medication. An overview of the five most widely used antihypertensive drugs will be provided, including beta-blockers, diuretics, calcium channel blockers, and ACE inhibitors. Herbal medicines have the potential to mimic, enhance, or counteract the effects of antihypertensive drugs. Existing literature on the topic is limited, consisting of both pharmacokinetic and pharmacodynamic interactions. Natural substances such as garlic, ginkgo, rose, guggul, piperine, capsicum, St. John's Wort, and grapefruit juice may alter the bioavailability, C_{max}, t_{max}, and AUC of antihypertensive drugs by affecting CYP 3A4 metabolism. Pharmacodynamic interactions have also been observed, such as the antagonistic effect between Spironolactone and Liquorice or the synergistic effect between Captopril and Garlic. Thus, caution is warranted to educate patients about the potential risks associated with combining herbal remedies and pharmaceutical drugs.

1. INTRODUCTION

Over the past few years, herbal medicines have become increasingly popular in many developing countries for treating various health conditions and promoting overall health [1,2]. This has opened up new avenues for research in the field. Notably, India stands out as a global biodiversity hotspot, with a diverse range of over 1740 medicinal and aromatic plant species that have been traditionally and modernly used for their therapeutic properties [3]. While herbs and herbal medicines have been used safely for centuries in traditional societies, combining them with pharmacological agents can potentially lead to interactions between the two. Around 15-20% of people taking prescription medications also use herbal supplements, but less than 40% disclose this use to their physicians, often due to concerns about criticism. Additionally, many physicians themselves may not be fully knowledgeable about the possibility for herb-drug interactions. Credible research is needed to assess the safety and effectiveness of combining herbs with pharmaceuticals [4].

The most prevalent cardiovascular disease is hypertension, characterized by blood pressure greater than 140/90 mm Hg for sustained periods of time. It represents a significant risk factor for stroke and contributes to conditions such as dissecting aortic aneurysms, heart failure, insufficient kidney function, and coronary artery disease [5]. Antihypertensive medications work by lowering blood pressure via impacting cardiac output, peripheral resistance, or both. Most individuals are treated for hypertension with diuretics, beta-blockers, ACE inhibitors, angiotensin II receptor blockers, and calcium channel blockers, among the nine different groups of antihypertensive medications [6]. The mechanisms underlying these interactions are still unknown,

despite a few published examples that were often poorly documented of herbal interactions with antihypertensive medications, including Ginkgo, Liquorice, Golden root, Grapefruit juice, Garlic, St. John's Wort, and Guggul [7].

The issue of herb-drug interactions can potentially have severe consequences. It is important to note that such interactions are not solely limited to chemical interactions between a drug and a specific component of an herb leading to toxic reactions [8]. Instead, these interactions can involve the herb component affecting the concentration of the drug in the bloodstream, either by increasing or decreasing it. Therefore, this review aims to provide a critical overview of the existing data on herb-drug interactions, drawing from in vitro experiments, animal studies, speculative evidence, and empirical observations. [9]

2. MECHANISMS DRUG-HERB INTERACTION

The idea of "possible interaction" refers to the possibility that when two drugs are taken together, one could alter the therapeutic effectiveness or bioavailability of the other. The interactions can be divided into two broad categories: pharmacokinetic and pharmacodynamic [10].

***2.1 Pharmacokinetic Interactions*:** When a drug and a herbal remedy are used together, pharmacokinetic interactions can affect how the drug is absorbed, distributed, metabolized, bound to proteins, or excreted. These interactions can lead to altered levels of the drug or its metabolites in the body [11]. The crucial pharmacokinetic phase of absorption is regulated by many variables, including gastrointestinal traits like pH and motility. Drug absorption may be impacted by herbal medicine's ability to change drug release mechanisms and ionizable drug solubility [12,13].

Transporter proteins play a significant role in drug absorption in the intestinal membrane. Influx carrier proteins such as PepT-1, ENT1,2, SGLT1, MCT1, OATPs, CNT1,2, and OCTN2, mediate the absorption of various compounds, including drugs. Efflux transporters are P-glycoprotein (P-gp or MDR-1), MRP-2 or ABCC2, and BCRP or ABCG2, which work to expel xenobiotics from enterocytes to prevent their absorption into the systemic circulation [14].

The oxidative metabolism of many drugs is carried out by cytochrome P-450 (CYP) enzymes, mainly CYP3A4. Herbal constituents can induce or inhibit CYP isoenzymes or efflux systems, thereby affecting drug metabolism and plasma concentration. For example, St. John's wort also helps to induce CYP3A4, reducing the plasma concentration of drugs metabolized by this enzyme [15-17].

Distribution interactions are less common but can occur when a drug has a limited therapeutic range and large protein-bound capacity. The effectiveness and safety of the medicine can be impacted by changes in distribution, such as modifications in protein binding. Warfarin is an example of a drug sensitive to modified distribution due to its high protein binding and narrow therapeutic range. Herb-drug interactions can also impact renal clearance. Herbs that inhibit tubular uptake or interfere with renal clearance may affect the elimination of drugs, leading to potential pharmacokinetic interactions [18].

Pharmacodynamic interactions involve the pharmacological activity of the interacting agents. Biologically identical to the targets of the drugs co-administered, herbal

medicine can mimic, enhance, or reduce the effects of those drugs in co-administered combinations. Synergistic or additive effects may enhance drug activity and lead to on-target toxicity. On the other hand, herbal medicines with opposing effects may reduce the effectiveness of medications and result in therapeutic failure. [19]

2.2 Pharmacodynamic Interactions: Pharmacodynamic interactions occur when herbs and drugs interact at the target site or receptor level, leading to additive, synergistic, or antagonistic effects. These interactions can enhance or diminish the therapeutic effects or adverse reactions of drugs [20]. Some examples of pharmacodynamic interactions include:

- Additive/Synergistic Effects: Herbs may enhance the therapeutic effects of drugs by acting on the same biological pathways or receptors, resulting in an additive or synergistic response [21].
- Antagonistic Effects: Conversely, herbs may antagonize the actions of drugs, reducing their efficacy or neutralizing their effects such as *Guarana (Paullinia cupana)* [22].
- Altered Adverse Reactions: Herbal substances can also modify the adverse reactions associated with certain drugs, either by exacerbating or mitigating their occurrence [22].
- For example, valerian can increase the hypnotic activity of benzodiazepines, while ginkgo and other herbs may enhance the anticoagulant action of warfarin. Conversely, herbs with high caffeine content, like Guarana, can antagonize the effects of sedative-hypnotics [19].

3. ANTİHYPERTENSİVE DRUG INTERACTİONS WİTH HERBAL TREATMENTS

3.1 Diuretics

Diuretics are effective in the treatment of hypertension by increasing urine volume and eliminating sodium, thus reducing blood volume. Thiazide diuretics, like hydrochlorothiazide, are commonly used for hypertension. [23,24] However, certain herbs can interact with diuretics:

- Ginkgo, a peripheral vasodilator, has been observed to cause a rise in blood pressure when taken along with thiazide diuretics. [25]
- Garlic, a popular herbal remedy with various health benefits, is widely consumed both as a food ingredient and a spice. This herb includes several volatile sulfur compounds, such as ajoene, diallyl disulfide, alliin, and allicin. The pharmacological properties of garlic include antiviral, antibacterial, antifungal, antihypertensive, blood pressure lowering, antithrombotic, antimutagenic, and antiplatelet actions. Garlic, however, interacts with hydrochlorothiazide like many other herbal medications. Because of this interaction, hydrochlorothiazide has a longer half-life and greater bioavailability, but its clearance and elimination rate constant are decreased [26 -28].
- Liquorice, often used as anti-inflammatory herb and an antispasmodic and, may diminish antihypertensive effects of spironolactone due to its potassium excretion mechanism. It can also produce additive effects when combined with other antihypertensive drugs that excrete potassium. [29,30]

- Roselle, known for its diuretic and antihypertensive properties, when co-administered with hydrochlorothiazide, can increase urine volume and alter urine composition, as well as prolong the plasma concentration of the drug [31].

3.2 Beta Blockers

Due to their long-term positive benefits on cardiovascular health, -blockers are frequently employed as the first-line therapy for hypertension. These medications decrease cardiac output, heart rate, and myocardial contractility [32]. However, certain herbal interactions have been identified:

- Piperine, when combined with propranolol, has been shown to enhance the systemic availability and overall exposure of the drug [33].
- Guggul is made from the Guggul tree's bark. Guggulipid is one of its functional ingredients. When Guggulipid was administered to normal volunteers along with propanolol, propranolol's peak plasma concentration (Cmax) and area under the curve (AUC) were significantly decreased as a result. This interaction suggests that co-administration of Guggulipid with propranolol in patients may show decreased effectiveness or insusceptibility due to a notable depletion in the bioavailability of propranolol. The pregnane X receptor may be activated by guggulsterone, which then upregulates the enzymes involved in the metabolism of propranolol as the underlying mechanism for this interaction. Studies conducted in rats have demonstrated that Guggulsterone administration lead to a significant increase in the expression of cytochrome P450 genes, which are critical to how different drugs are metabolized [34,35].
- Garlic homogenate and propranolol have been used in combination therapy, which has been shown to promote systolic blood pressure reduction by increasing the drug's bioavailability and half-life while lowering its clearance and elimination rate constant [36].

3.3 ACE Inhibitors

- ACE inhibitors are frequently provided to patients who have ischemic heart disease and hypertension as part of their treatment. When used right away after a myocardial infarction, ACE inhibitors, such as Captopril, have been shown to enhance ventricular function and reduce morbidity and mortality. A typical medication for controlling hypertension and congestive heart failure is captopril, an angiotensin-converting enzyme inhibitor.
- A synergistic effect is seen when captopril is given along with fresh garlic homogenate or its active ingredient, S-allyl cysteine. This combination results in enhanced antihypertensive and cardioprotective effects. The concurrent use of captopril with Garlic or S-allyl cysteine demonstrates a beneficial interaction, potentially leading to improved blood pressure control and protection of the heart.
- This interaction between captopril and Garlic or S-allyl cysteine highlights the potential for utilizing herbal remedies as adjunctive therapy to standard pharmacological treatments. By combining these substances, healthcare professionals can optimize treatment outcomes and provide additional benefits to patients with hypertension and ischemic heart diseases [37].
- The employ of angiotensin-converting enzyme (ACE) inhibitors for therapeutic purposes can lead to the occurrence of a dry cough as a common side effect.

The localized rise of substance P or bradykinin concentrations in the lung is thought to be the mechanism underlying this aggravated cough symptoms with ACE inhibition [38]. Therefore, when Capsicum, a substance known for its spicy properties, is consumed in conjunction with ACE inhibitors, there is a potential risk of developing cough symptoms. It's crucial to be aware of this interaction because taking ACE inhibitors and capsicum together may make it more likely that coughing-related adverse effects [39].

3.4 Angiotensin-II Receptor Blockers (ARBs)

Angiotensin-II receptor blockers are commonly employed to regulate cardiovascular function. Certain herbal interactions have been identified:

- The development of nonpeptide antagonists targeting the AT1 angiotensin II receptor has revolutionized the treatment of hypertension. The regulation of cardiovascular function is frequently achieved with the use of medications like Losartan, Candesartan, Irbesartan, Valsartan, Telmisartan, and Eprosartan. However, when the herbal product such as *Rhodiola rosea* is administered alongside Losartan, there is a notable increase in the area under the curve, maximum plasma concentration (Cmax), and apparent total body clearance (CL/F) of Losartan in rabbits. This interaction is significant as both Losartan and Rhodiola rosea are substrates of CYPs (cytochrome P450 enzymes) and P-gp (P-glycoprotein). Therefore, caution should be exercised when combining these substances, considering their potential impact on the pharmacokinetics and effectiveness of Losartan [40].

3.3 Calcium Channel Blockers

Because of their efficiency and low frequency of side effects, calcium channel blockers (CCBs) are frequently used to treat a variety of cardiovascular diseases. They are frequently recommended for angina, hypertension, and supraventricular arrhythmias. Phenyl alkylamines, benzothiazepines, and dihydropyridines are the three main classes of CCBs, and examples of each include Verapamil, Felodipine, Nicardipine, Nifedipine, and Nimodipine. [41,42].

- Elderly people frequently take ginkgo to increase blood flow and cognitive performance in people with illnesses including Alzheimer's disease, dementia, peripheral vascular disease, tinnitus, or memory loss. Studies have demonstrated that combined administration of Ginkgo and Diltiazem in rats increased the drug's bioavailability by preventing its absorption through the gut and liver. This inhibition is thought to be caused, at least in part, by CYP3A4 enzymes being inhibited by a mechanism. Nifedipine, a CYP3A4 substrate, is likewise less metabolized by ginkgo, which results in higher levels of Nifedipine [43,44].
- Grapefruit juice has been found to hinder intestinal CYP3A4 enzymes, causing increased drug levels of oral preparations. This interaction is more pronounced with calcium channel blockers that have high bioavailability, such as Amlodipine and Diltiazem, compared to those with lower bioavailability like Felodipine and Nisoldipine. Grapefruit juice has a less significant impact on these medications' intravenous formulations [17].
- St. John's wort, a popular plant-based antidepressant, induces CYP3A4 enzymes and P-glycoprotein, leading to altered pharmacokinetics of various

drugs. St. John's wort may accelerate the metabolism of the calcium channel blocker Nifedipine by promoting the activity of the CYP3A4 enzyme when combined with Nifedipine. [45].

- Another calcium channel blocker called verapamil works to lower arterial pressure by preventing calcium ions from entering vascular smooth muscle cells, which lowers smooth muscle tone and vascular resistance. It has been demonstrated that taking St. John's wort along with verapamil reduces both the R- and S-verapamil's bioavailability. This result corresponds to the stimulation of CYP3A4 metabolism, which most likely takes place in the stomach. Incompatibilities between herbal medicines (like Ginkgo and St. John's wort) and calcium channel blockers can significantly impact the pharmacokinetics and effectiveness of the drugs [46]. **Table 1** presents a compilation of herbal remedies that have been implicated in interactions with antihypertensive drugs.

Herbal remedies that interact with antihypertensive drugs are listed in Table-1.

Antihypertensive Class	Interacting Drug	Herbal Drug	Interaction results	References
Diuretic	Thiazides	*Ginkgo biloba (Ginkgo)*	Increased blood pressure	27
		Allium sativum (Garlic)	Reduced clearance and elimination rate combined with increased bioavailability and half-life of hydrochlorothiazide	28
		Hibiscus sabdariffa (Roselle)	Increased urine output, a reduction in urine's pH and sodium, bicarbonate, and chloride ion concentrations, and a prolongation of hydrochlorothiazide's Cmax, the area under the curve and Vd all contribute to an increase in urine output.	31
	Spirnolactone	*Glycyrrhiza glabra (Liquorice)*	Antagonistic effect	29
	Antihypertensive Drugs		Additive effect	30
β-Blockers	Propanolol	*Piper nigrum (Black Piper)*	Tmax, Cmax, and AUC rise as a result of CYP 1A2 inhibition.	33
		Commiphora mukul (Guggul)	lower bioavailability, decreased Cmax, and decreased AUC	34
		Allium sativum (Garlic)	Decreased clearance and constant elimination rate, as well as an increase in	36

			bioavailability and half-life	
ACE Inhibitor	Captopril	*Allium sativum (Garlic)*	Enhancing their properties as Synergistic antihypertensive effect	37
		Capsicum annum (Capsicum)	May cause cough	39
Angiotensin-II Receptor Blocker	Losartan	*Rhodiola rosea (Golden root)*	Elevation Cmax, AUC, and CL	40
Calcium Channel Blocker	Diltiazem	*Ginkgo biloba (Ginkgo)*	Increased medication bioavailability caused by CYP3A4 inhibition	44
	Felodipine	*Citrus paradisi (Grapefruit juice)*	Help to Increase the bioavailability of Felodipine.	17
	Nifedipine	*Hypericum perforatum (St. John's Wort)*	May Decreased Cmax and AUC through induction of CYP3A4.	45
		Ginkgo biloba (Ginkgo)	May cause Decrease in metabolism of Nifedipine by inhibiting CYP3A4, increased Cmax	17
	Verapamil	*Hypericum perforatum (St. John's Wort)*	May Decreased the bioavailability of verapamil through induction of intestinal CYP3A4	46

4. RISK ASSESSMENTS [47,48]

Assessing the risk of interactions between antihypertensive drugs and herbal drugs is an important aspect of patient safety and medication management. The risk assessment involves evaluating the potential for interactions based on available scientific evidence, clinical studies, and expert opinions. Here are some key points to consider in the risk assessment process:

4.1. Mechanism of Action: Understand the mechanism of action of both the antihypertensive drug and the herbal drug. Identify any shared or overlapping pathways that could potentially lead to interactions.

4.2. Pharmacokinetic Interactions: Assess whether the herbal drug affects the absorption, distribution, metabolism, or elimination of the antihypertensive drug. Look for potential inhibition or induction of drug-metabolizing enzymes, such as CYP450 enzymes, which can alter the pharmacokinetics of the antihypertensive drug.

4.3. Pharmacodynamic Interactions: Evaluate whether the herbal drug has additive, synergistic, or antagonistic effects on blood pressure control when used concomitantly with the antihypertensive drug. Consider factors such as vasodilation, diuretic effects, or impact on cardiac function.

4.4. Available Evidence: Review published literature, clinical trials, case reports, and drug interaction databases for information on documented interactions between the specific antihypertensive drug and herbal drug. Look for consistent findings and evaluate the strength of the evidence.

4.5. Dose and Duration: Consider the dosage and duration of use for both the antihypertensive drug and the herbal drug. Higher doses or prolonged use may increase the likelihood of interactions.

4.6. Patient Characteristics: Take into account individual patient factors such as age, overall health status, hepatic or renal function, and any known drug allergies or sensitivities. Certain patient populations may be more susceptible to interactions.

4.7. Professional Guidance: Consult with healthcare professionals, such as pharmacists or physicians with expertise in herb-drug interactions, to assess the risk and determine the appropriate course of action. They can provide personalized recommendations based on the patient's specific circumstances.

4.8. Monitoring and Communication: Establish a plan for monitoring the patient's response to the antihypertensive drug and herbal drug combination. Encourage the patient to share any concerns, negative side effects, or changes in blood pressure during the course of medication.

5. CONCLUSION

Remember that the risk assessment should be an ongoing process, as new evidence and information may emerge over time. It is important to stay updated with the latest research and regulatory guidelines regarding drug-herb interactions.

In conclusion, the relationship between herbal medicine and antihypertensive medications is a complex and developing area that needs careful examination. The topics discussed shed light on various important aspects and future perspectives related to this interaction.

One crucial aspect is risk assessment. Assessing the potential risks associated with interactions between antihypertensive drugs and herbal medicine is essential to ensure patient safety. Factors such as pharmacokinetic and pharmacodynamic interactions, herbal potency, and individual patient characteristics need to be taken into account.

Understanding the mechanisms underlying herb-drug interactions and identifying biomarkers for prediction and monitoring is an area that requires further research. Elucidating these mechanisms can help healthcare professionals make informed decisions and tailor treatment approaches based on individual patients' genetic profiles and susceptibility to herb-drug interactions.

Standardization and quality control of herbal preparations are vital to ensure consistent quality, potency, and safety. Establishing manufacturing processes and regulatory guidelines can minimize variations and improve predictability in the herbal products market.

Integrative approaches that combine traditional medicine knowledge with scientific methodologies can enhance our understanding of herb-drug interactions. Collaboration between traditional medicine practitioners and modern healthcare professionals can lead to a comprehensive and holistic approach to patient care.

Conducting well-designed clinical trials and gathering robust evidence is crucial in guiding healthcare professionals when considering the combination of antihypertensive drugs and herbal medicine. Evidence-based practice ensures that decisions are based on solid scientific evidence and contribute to improved patient outcomes.

Establishing pharmacovigilance systems and reporting mechanisms is important for capturing and monitoring adverse events related to herb-drug interactions. This proactive approach enhances patient safety by identifying and addressing potential risks promptly.

Patient education plays a vital role in promoting the safe use of antihypertensive drugs and herbal medicine. Increasing patient awareness about potential interactions and the importance of open communication with healthcare professionals empowers individuals to make informed decisions regarding their medication and herbal supplement use.

In conclusion, addressing these topics and considering future perspectives in the case of antihypertensive drug and herbal medicine interactions can contribute to improved risk assessment, personalized medicine approaches, evidence-based practice, and enhanced patient care and safety.

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