CHAPTER EIGHT

CLINICAL EVIDENCE: EFFICACY OF HERBAL-SYNTHETIC SYNERGIES

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Abstract

The increasing popularity of natural and conventional medicinal products has led to a growing interest in phytomedicine, particularly the synergistic effects of plant extracts. This chapter explores the mechanisms of synergy among herbal compounds and their interactions with synthetic drugs, highlighting the potential benefits and risks associated with their combined use. While the synergistic properties of multi-targeted herbal extracts can enhance therapeutic efficacy beyond that of individual components, concerns regarding safety and adverse effects persist. The study categorizes herb-drug interactions into pharmacokinetic and pharmacodynamic types, elucidating how these interactions can alter the metabolism and efficacy of conventional medications. The important interactions of certain herbs, like garlic, kava, and St. John's wort, with different drug classes—such as those that impact the cardiovascular system, central nervous system, and hypoglycemic agents—are investigated. The findings underscore the necessity for greater awareness and reporting of herbal medicine use among patients to mitigate potential adverse interactions and maximize therapeutic outcomes. This comprehensive chapter aims to provide insights into the complexities of herbal-synthetic synergism and its implications for clinical practice.

Keywords: Interaction, Synergism, Herbs, Clinical evidence,

Introduction

Natural and conventional medicinal products have been popular since the late 19th century and are widely used today. As people's interest in these products grows, many associate natural and herbal terms with safety and protection. In the past few years, phytomedicine's synergistic study has emerged as a significant emerging field. The increased efficacy of multiple plant extracts is attributed to the synergistic effects of the combination of medicinally active components and their metabolites (Stermitz et al. 2000; Williamson 2001). As a result, the use of herbal medications has increased significantly around the world. Some herbs contain lower concentrations of active components than the therapeutic dosages typically required, which has led to scepticism and the theory that the effects of placebo might be the source of the benefits attributed to herbal medicines (Lewith, Hyland, and Shaw 2002). Nevertheless, studies show that the entire range of herbal medicine's constituents can work much more effectively than a single active ingredient of the same volume. Synergy occurs when two or more herbal substances work together to enhance each other's effects beyond what they would achieve alone.

Herbal remedies and medications derived from natural sources might nonetheless have negative adverse reactions and responses. Herbal drugs have been linked to some symptoms, including hives, uneasiness in the stomach, diarrhea, vomiting, allergens, migraines, etc. Some herbs may potentially be poisonous and possibly fatal to people. The modes of action of synergistic drug combinations have been studied using network-regulatory actions and molecular interaction profiles mediated by the drugs. The same methodology is used to examine the accumulated insights of different medicinal compounds, and their ingredient-mediated profiles can also be used to investigate possible examples and strategies of synergy among medicinal compounds.

Synergistic multi-targeted effects

The components of a single-extract or multi-extract combination act agonistically and synergistically, influencing several targets rather than just one. Researchers have discovered potentially important drug targets using approved therapeutic ingredients like digestive enzymes, substrates, metabolites, amino acids, receptors, electron transport molecules, RNA, DNA, ribosomes, immunoglobulins, and physical mechanisms. As shown in Fig. 1, compounds composed of single extracts targeting only one specific receptor will produce an agonistic effect. However, if the individual components interact with multiple targets, they can create potent synergistic effects. In such cases, the total effects may be several times greater than the value of the combined individual synergistic effects.

Synergism has three types of mechanisms that affect the drug- (Pezzani et al. 2019; Rai et al. 2021)

Multi-targeting: Medications that target multiple proteins or pathways may have a broader healing impact. In cancer therapy, for example, multi-targeted drugs have shown potential in regulating key molecules that control cell cycle barriers.

Pharmacological sciences: This approach considers the entire network of chemical interactions, replacing the traditional 'one-drug, one-target' methods with a more holistic strategy. Frameworks biology tools enable researchers to uncover beneficial links between various medications and their effects.

Multimodal counseling: Combining different medications can improve selectivity and lessen the negative effects of high dosages of single-target medications. This can be especially helpful in combating multidrug resistance in chemotherapy for cancer.

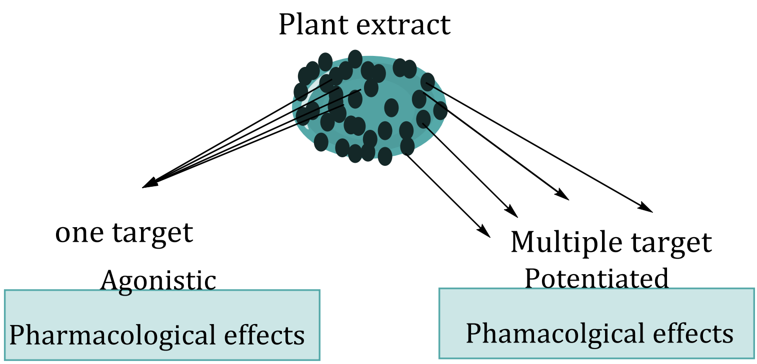

Fig. 8-1 An imagined and simple visual representation of the single- and multi-target effects produced by a single extract that contains many ingredients and aims towards one or more cell targets.

General Mechanism of Herbal-Synthetic Synergism

Interactions between herbs and drugs can produce different effects. They may have an antagonistic effect, which reduces the medication's effectiveness, or a synergistic effect, which enhances the drug's activity. Additionally, these interactions can alter the impact of one or both substances. Herbal medications adhere to contemporary pharmacological standards. As a result, the pharmacokinetic and pharmacodynamic mechanisms underlying interactions between drugs also apply to herb-drug interactions.

The combination occurs at each stage of the medication's biosynthesis processes, which alters the amount of the drug at the site of activity or in the blood. In general, there are two main categories of herb-drug interactions.

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Pharmacokinetic interactions

Change the drug's plasma concentration.

Pharmacodynamic interactions

Targets organs sensors at the site of interactions.

Pharmacokinetic Interactions

This category can be used to group all interactions that result from changes in absorption, disruptions in drug distribution structures, and antagonism in biochemical or elimination pathways. Substance transport proteins like P-glycoprotein or drug-metabolizing enzymes like cytochrome P450 are more likely to be induced or inhibited as a consequence of these. Each of them is essential for drug absorption.

According to more thorough research on pharmacokinetic interactions and in vitro and in vivo studies, the stimulation of liver and digestive drug-metabolizing enzymes, especially cytochrome P450 (CYP), and medication transporters like P-glycoprotein may be responsible for the changed drug concentrations caused by mixed herbs.

Cytochrome P450 (CYP) Enzyme Interaction

The crucial stage of the drug-metabolizing protein framework, the CYP, is in charge of many different medications' metabolism. Many natural substances that have been extracted from herbs, such as flavonoids, coumarins, alkaloids, and terpenoids, as well as herbs like St. John's wort, echinacea, kava, and garlic cloves, are substrates, inhibiting agents, and stimulants of different Cytochrome enzymes (Ioannides 2002). Because cytochrome P450 enzymes metabolize some medications, St. John's wort has been shown to impact their plasma levels.

CYP enzymes play a crucial role in the metabolism of many medications and are produced in the gut and the liver. These enzymes are categorized into different groups, with CYP1, CYP2, and CYP3 particularly important for drug metabolism. Within these groups, specific enzymes such as CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 predominantly participate in metabolizing drugs. Interactions with these enzymes can lead to variations in digestion, differences in transport sequences, or changes in metabolic pathways and elimination routes (Fasinu, Gurley, and Walker 2015; Colalto 2010).

P-Glycoprotein Interaction

Drug transporter proteins significantly affect a drug's pharmacokinetics based on its location within the human body. They affect how a drug enters the bloodstream, travels through the intestines, and leaves the body. Thus, these proteins aid in controlling the drug's plasma concentration and bioavailability. P-glycoprotein, a crucial transporter protein, affects how medications are absorbed, distributed, and eliminated and may have many interconnected effects. This carrier enzyme affects drug metabolism by increasing drug excretion from liver and kidney tubules into the surrounding lumen region and restricting the movement of drugs from the lumen of the gut into epithelial cells (Lin and Yamazaki 2003).

Pharmacodynamic Interactions

These relationships result from molecules interacting with receptor sites or from varying degrees of biological surrounding adaptation. Herb-drug interactions at the receptor level might be antagonistic, meaning the herb may lessen the effects of a concurrently delivered drug, or 'synergetic,' which increases the pharmacological/toxicological activity of artificial pharmaceuticals. Vitamin K-containing plants can reduce the clotting impact of warfarin, while coumarin-containing plants may boost it (Fasinu, Gurley, and Walker 2015; Bernardo and Valentão 2024).

Antagonistic Interactions

Inevitably, an herb may have the opposite effect from the one intended for the medicine, lessening its effects. Ephedra or herbs that contain caffeine, such as green tea, marijuana, and walnut, are frequently combined. Many natural shedding pounds remedies have additive cardiovascular hazards that could counteract the effectiveness of anticoagulant drugs (Barnes 2011).

Additive Interactions

Concurrent use of antihypertensives, natural tranquilizers, and blood thinners may intensify the effects of typical medications for the same reason. For instance, ginger, ginkgo, and clove all improve the clotting effect of warfarin. Likewise, chamomile enhances diazepam's drowsy effects (Silva et al. 2024).

Adverse Effects and Limitations

Herbs can have undesirable side effects, including toxicity, similar to any other therapeutic substance. The side effects of herbs may be influenced by factors such as the consumer's gender, age, genetics, dietary habits, and existing medical treatments. Currently, there is limited evidence-based knowledge regarding the toxicity of herb-drug interactions. Much of what we know is based on conjecture or hypothetical mechanisms, many of which have only been observed in vitro (in a controlled environment) rather than in vivo (in a living organism).

To understand the toxicological consequences of any medicinal products, particularly contemporary prescription medications. Interactions between herbs and drugs can adversely affect various organs, including the heart, gastrointestinal tract, kidneys, and skin. It is advisable to avoid using ginseng alongside other medications that are known to be toxic to the liver due to their significant harmful effects (Anastasi, Chang, and Capili 2011; Williams 2021).

Synergism of Mostly Used Herbal with Synthetic

The possibility of a potential herb-drug combination cannot be eliminated, even when herbal medications or preparations are believed to be harmless. The more than 35,000 herbal preparations containing more than 1000 different chemical compounds increase the risk of herb-drug interactions. Below is a discussion of some common herbs and the potential consequences of medication interactions (Hussain 2011; Ismail 2009).

St. John's Wort

St. John's wort (*Hypericum perforatum*) has been historically suggested for various illnesses, but it is most commonly used to alleviate feelings of melancholy. Research has shown that St. John's wort increases the transcription of P-glycoprotein both in vitro and in vivo (Semeláková, Jendželovský, and Fedoročko 2016; Borrelli and Izzo 2009). Additionally, St. John's wort can reduce the absorption of antibiotics, anticoagulants, and other medications, leading to potential negative interactions when taken alongside oral contraceptives or pills (Velingkar, Gupta, and Hegde 2017).

Saw Palmetto

In the U.S., saw palmetto (*Serenoa repens*) is commonly used to treat benign prostatic hyperplasia (BPH). In addition to its antibacterial properties, it can also be used as an alkaline solution to treat urinary tract infections. According to in vitro studies, saw palmetto blocks alpha receptors for adrenergic stimuli, which may be the cellular mechanism behind its effectiveness as a therapy (Tachjian, Maria, and Jahangir 2010; Barnes 2011).

Kava Kava

Kava kava (*Piper methysticum*) is a well-known anxiolytic and central nervous system (CNS) depressant. The primary active compounds in kava, known as kavalactones, are believed to be strong inhibitors of the CYP450 enzyme. As a result, there is a considerable risk of pharmacokinetic interactions when Kava is used in conjunction with other CNS depressant medications. It is not recommended to take kava with these medications or any other medications that are metabolized by the same CYP450 enzyme due to the evidence of significant interactions (Savage et al. 2018; Singh 2005).

Echinacea

Echinacea is derived from the *Echinacea purpurea* plant; however, individuals with HIV often use other Echinacea species as an immunostimulant to quickly address pneumonia in the upper respiratory tract. Clinical research indicates that mixing different Echinacea species does not affect the metabolism of antiretroviral medications, such as ritonavir or darunavir, and has not shown any negative effects (Ladenheim et al. 2008; Sharma et al. 2010).

Grouping of Herbal-Synthetic Synergism by Employing Clinical Drug

Classifying the vast amount of accessible data into manageable categories is essential for a deeper understanding of any investigation. Certain plants can interact with conventional medications, altering the medications' therapeutic effects and potentially leading to clinical manifestations. Today, underreporting of herbal medication use by patients is a major problem that ultimately impacts traditional treatment plans. This study attempts to classify herbal interactions with conventional medications according to pharmaceutical therapeutic classifications.

Only the most promising therapeutic classes with potential clinical effects and substantiating scientific evidence are highlighted, though several classes of synthetic medications may interact with herbs.

Interactions with drugs affecting the central nervous system

A depressive disorder that is from mild to profound can be effectively treated with the herb St. John's wort. Aside from being a P-glycoprotein substrate, St. John's wort can additionally activate CYP2C19 and CYP3A4 to trigger the removal of methyl groups and consequent hydroxylation of amitriptyline. Additional plants that interact with medications contain Echinacea, Primrose oil, garlic, ginseng, aloe vera, Shankhapushpi, ginkgo, and diuretics function differently (Di Carlo et al. 2001).

Table 8-1 Herb-drug interaction affecting the central nervous system

Drug	Herb/plant	Result	Mechanism
Caffeine	Echinacea	Decreases	Echinacea inhibits caffeine, a substrate of CYP1A2.
Alprazolam	St John's wort	Low plasma level	Alprazolam-specific CYP3A4 probe triggered by St. John' wort
Phenytoin	Shankhapushpi	Decrease in seizure control	Not known accurately
Levodopa	Kava	Low efficacy	Kava dopaminergic antagonistic effects
Fluphenazine	Primrose oil	Seizures	Gamalenicacid primrose oil reduces the threshold for seizures.

Interactions with drugs affecting the cardiovascular system

Multiple plants interact differently with some heart disease medications, such as ventricular inotropic, blood thinners, anti-hyperlipidemia, and high blood pressure medications. St. John's wort (Hypericum perforatum) can interact with various medications by inducing the CYP enzymes and P-glycoprotein. This induction results in lower blood concentrations of those medications. Additionally, ginkgo biloba may enhance the effects of certain drugs through pharmacodynamic interactions or interactions with P-glycoproteins. Herbs like ginseng, devil's claw, fenugreek, garlic, boldo, and cranberries can also increase the effects of blood thinners like warfarin (Jiang et al. 2004).

Table 8-2 Herb-drug interaction affecting the cardiovascular system

Drug	Herb/plant	Result	Mechanism
Warfarin	Fenugreek, cranberry, garlic, ginkgo, ginseng, wolfberry, papaya,	Excessive anticoagulation	Cumulative effects on clotting processes in general. These herbs may have antiplatelet (garlic, ginseng) or anticoagulant (fenugreek) qualities. Cranberry polyphenols could block CYP enzymes, among other methods.
Lovastatin	Pectin	Reduce absorption	Lovastatin is trapped in the gut by pectin
Simvastatin	St. John’s wort	Low plasma	St. John's wort induces P-glycoprotein and CYP enzymes, which are involved in the breakdown of simvastatin.
Digoxin	Wheat bran	Low plasma concentration	Collect in gut
Aspirin	Ginkgo	Random hyphema	Additive effect on platelet aggregation

Interactions with drugs affecting the hypoglycaemic system

Garlic and bitter gourd are two herbs that were once used to regulate insulin levels. However, some herbs can change the adverse reactions of some diabetic drugs through interaction. Gums may have an impact on the assimilation of concurrently administered drugs, especially hypoglycemic drugs, owing to their ability to prolong stomach persistence and the fact that medications diffuse more slowly through viscous structures than from solutions (Capasso 2003).

A forty-year-old woman with diabetes who is taking chlorpropamide and medication containing garlic has been reported to experience a drop in her blood sugar levels. This drop is likely due to the cumulative effects on her blood glucose levels, as garlic is known for its hypoglycemic properties (Aslam and Stockley 1979).

Table 8-3 Herb-drug interaction affecting the hypoglycaemic system

Drug	Herb/plant	Result	Mechanism
Chlorpropamide	Garlic	Low blood sugar	Not known
Ginkgo	Tolbutamide	Lower blood level	Not Known
St. John's wort	Gliclazide	Lower blood level	Initiation of CYP
Opuntia	Metformin	Hypoglycaemia	Cumulative effect

Interactions with drugs affecting the antiretroviral and anticancer drugs

Irinotecan, an antagonist of SN-38 and a known substrate of CYP3A4, is primarily used to treat colorectal cancer. A random, non-blinded overlap study involving five melanoma patients found that St. John's wort reduced the blood levels of the active metabolite SN-38 by 40%. Consequently, the incidence of myelitis was significantly higher when St. John's wort was not taken. After receiving garlic repeatedly, ten healthy individuals showed a substantial decrease in their bloodstream levels of the protease blocker saquinavir (Henderson et al. 2002).

Table 8-4 Herb-drug interaction affecting the antiretroviral and anticancer drugs

Drug	Herb/plant	Result	Mechanism
Imatinib	Ginseng	Hepatotoxicity	Not known
Saquinavir	Garlic	Lower blood concentration	Initiation of P-glycoprotein in the gut
Irinotecan	St. John's wort	Lower blood concentration	CYP3A4 interaction
Ritonavir	Cat's claw	Raised blood level	Not known

Interactions with drugs affecting the immunosuppressants

One of the most dangerous—and potentially lethal—interactions between conventional medications and herbal remedies occurs between cyclosporine and St. John's wort. This interaction is well documented, with multiple instances and case series reported. In one case, a 54-year-old kidney transplant patient experienced a sudden increase in their cyclosporine blood level after consuming red avens, which rose to between 470 and 600 mg/dL. Once the herb was discontinued, the blood levels returned to a normal range of 55 mg/dL(Surana et al. 2021).

Table 8-5 Herb-drug interaction affecting the immunosuppressants

Drug	Herb/plant	Result	Mechanism
Cyclosporine	St. Jonh's wort	Lower blood level	Initiation P-glycoproteins/CYP
Tacrolimus	Magnolia berry	Increased blood level	Block P-glycoproteins
Cyclosporine	Red avens	Increased blood concentration	Unknown
Cyclosporine	Red yeast rice	Muscle necrosis	Concentration levels increased cyclosporine suppresses CYP3A4

Conclusion

The chapter focuses on the possible health advantages of herbal compounds and the related safety concerns. It highlights the importance of understanding the synergistic effects that can occur when these herbal remedies are used alongside synthetic pharmaceuticals. The chapter encourages improved patient education and communication regarding the use of herbal medicines to decrease adverse interactions and enhance treatment outcomes.

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