HASIL CEK_Herbal Synthetic Drug Interaction

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Herbal - Synthetic Drug Interactions

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Abstract

Background: Herbal medicine is currently one of the therapeutic options chosen by the community because it is considered relatively safer and has minimal side effects. Not only used as a single drug, but herbal ingredients can also be combined with synthetic drugs. However, using herbal and synthetic drugs simultaneously can cause a variety of interactions, including synergism, antagonism, and additive effects (potentiation).

Objective: Therefore, it is crucial to do a literature study on the reaction of various herbal medicines to unwanted synthetic drugs to prevent the adverse effects that can be caused.

Methods: The literature review is processed based on academic journals published on NCBI, PubMed, and online journal sources that discuss the interactions between herbal medicines and synthetic drugs from 1997 to 2022.

Results: Herbal drug interactions can be avoided or managed by providing correct patient advice based on reliable information.

Conclusion: The main basic principles of administering these medicines include the doctor's full awareness of the effects and interactions between herbal medicines and herbal medicines and herbal medicines with synthetic drugs.

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INTRODUCTION

Traditional medicine is an ingredient derived from plants, animals, minerals, or a mixture of these materials, which is usually used for generations for treatment, disease prevention, and health maintenance. Currently, the use of traditional medicine is increasing in both developing and developed countries. Each country or region has different habits in using traditional medicine because it is influenced by several factors such as culture, history, and individual attitudes. The most widely used traditional medicines worldwide are herbal medicines derived from plants.[1]

In the beginning, the principles of conventional medicine were intensively developed. However, due to reports of high side effects associated with these synthetic drugs, public attention has recently become more open to using herbal substitutes to prevent the side effects of synthetic drugs.[1]

Traditional medicine can also cause side effects, although not for everyone. Patients from among children, the elderly, and immune-compromised are more susceptible to experiencing side effects from the herbal medicines consumed. When consuming herbal medicines, a complex mixture will be formed between the compounds in the body and those in herbal medicines.[1]

A relevant safety issue related to herbal medicines is the risk of interaction between herbal and synthetic drugs prescribed by doctors and self-medication.[2] These interactions are essential for drugs with a narrow therapeutic index, such as warfarin or digoxin.[3] Recent examinations show that 16% of patients who get drugs from doctors will take herbal supplements. This result is compounded by the many herbal medicines marketed online with misleading and unproven claims. People think herbal medicine (natural) has no side effects or is safe to use. The high use of herbal medicines and the increasing reports of side effects of herbal medicines requires a better understanding of the potential for interactions between herbal medicines and synthetic drugs by health professionals.

METHODS

The method of writing this article review is in the form of literacy studies from various journals explored by NCBI, Pub Meb, and other online journal sources that discuss interactions between herbal medicines and synthetic drugs. This literacy study uses articles published between 1997 and 2022. The search keywords used are ethnomedicine, herbal medicine, synthetic drugs, and drug interactions. A search for scientific journals regarding medicinal plant research discussed in this article review was conducted in August 2022. The inclusion criteria in this article were research articles published from 1997 to 2022, international research articles, and ethnomedical and phytochemical research. The exclusion criteria were articles published on social media, not journals, personal websites, or blogs.

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RESULTS

Plants have been used to treat ailments since ancient times and are a major source of modern single-compound drugs.[4] Herbal medicines continue to be widely used globally because of certain health beliefs and because more and more scientific information is available about their patient benefits and safety. While it is true that many plants that have been used traditionally for therapeutic and culinary applications are generally safe, it is also essential to recognize that some plants are highly toxic and can even be deadly. When patients take herbal medicines in conjunction with prescribed allopathic drugs, interactions can occur between the phytochemicals in the herbal medicines and the active ingredients of the prescription drugs through several mechanisms, which can be defined as pharmacokinetic or pharmacodynamic. These interactions may impact pharmacological activity, blood levels, metabolism, or toxicity of allopathic drugs.[4,5] Herbal drug interactions are based on the same pharmacological principles as drug-drug interactions.[4]

In contrast to single compounds containing allopathic drug products, herbal medicines contain a complex mixture of phytochemicals produced usually as secondary metabolites. Herbal medicines (e.g., extracts or plant ingredients) can easily contain more than 150 ingredients, making identifying factors causing side effects and interactions difficult.[4] In addition, side effects due to herbal drug interactions are generally underreported and documented, a problem exacerbated by a lack of disclosure by patients about their use to their healthcare providers.

Interactions are said to occur when the presence of another drug, food, or drink changes the effect of one drug. While the therapeutic combination may cause unexpected changes in the patient's condition, these are potentially clinically significant interactions. The effects of this drug combination can be synergistic or additive effects of one or more drugs, antagonistic effects of one or more drugs, changes in the effects of one or more drugs, or the production of idiosyncratic effects. Drug-drug interactions can be defined as the effect of one drug on another.

Some things that can cause interactions between herbs and synthetic drugs include:[1]

1. The general perception of people is that herbal products do not cause any side effects.
2. Pharmacokinetic and pharmacodynamic interactions related to herbs and drugs are still unknown and have little information or literature.
3. Herbs consist of several compositions and compounds that increase the possibility of unwanted reactions.
4. Lack of literature discussing the evidence base, doses, and routes of herbal administration, formulas, and the herbal medicines themselves.
5. Lack of standardization, counterfeiting of goods, and contaminated products.
6. Doctors unaware of the use of herbs by patients and know about herbs can differ between regions.

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Table 1. List of Herbal Interactions with Synthetic Drugs

Synthetic Drugs	Herbs	Herbs Dose	Pharmacokinetic Interaction	Pharmacodynamics Interaction	Reference
Metformin	*Aloe vera* (aloe vera)	Dosage information is not available	Decrease Disolution metformin	Synergist	5
	Momordica charantia (bitter melon)	Dosage information is not available	Not available	Synergist	5
	Cinnamomum verum (cinnamon)	300-600 mg/kg/day	Not available	Synergist	5
	Trigonella foenum graecum (klabet seeds)	2g/day	Not available	Synergist	5
	Allium sativum (garlic)	500 mg/kg	Not available	Synergist	5
	Andrographis paniculata (whileoto)	434,6 mg/kg	Reduces the bioavailability of metformin	Antagonist	5
	Maringa oleifera (moringa leaf)	375-1.500 mg/kg	Not available	Synergist	5
	Gymnema sylvestre (gurmara)	Dosage information is not available	Slower to reach maximal concentrations and distribution of metformin	Antagonist	5
Glibenclamide	*Allium sativum* (garlic)	500 mg/kg	Not available	Synergist	5
	Cinnamomum cassiea (chineese cinnamon)	60 mg/kg	Not available	Synergist	5
	Aloe vera (aloe vera)	Dosage information is not available	Not available	Synergist	5
	Coccina indica (tropical grapes)	200 mg/kg	Not available	Synergist	5
	Andographis paniculate (whileoto)	Dosage information is not available	Not available	Synergist	5
Pioglitazone	*Aloe vera* (aloe vera)	Dosage information is not available	Not available	Synergist	5
Tacrolimus	*Tumeric*	Dosage information is not available	Decrease metabolism Tacrolimus	Not available	4

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Warfarin	*Ginger*	Dosage information is not available	Not available	Synergist	7
	Peppermint Tea	Dosage information is not available	Not available	synergist	7
Antacid	*Peppermint oil*	Dosage information is not available	Damage enteric coating peppermint oil	Not available	8
Paracetamol	*Parsley*	Dosage information is not available	Not available	Synergist	8
Aspirin	*Coffee*	200 mL coffee	Decrease absorption of aspirin by 30%	Not available	8

Interactions between herbs and synthetic drugs can be classified into 2, namely:[1]

1. Synergist and antagonist
2. Positive and negative

Herbal medicines follow modern pharmacological principles. Therefore, herbal-synthetic drug interactions can be characterized by either pharmacokinetic or pharmacodynamic mechanisms.[6] Pharmacokinetic interactions specifically refer to changes (i.e., enhancement or inhibition) in the absorption, distribution, metabolism, and excretion of drugs elicited by co-administered herbal drugs, whereas pharmacodynamic interactions include synergistic or antagonistic pharmacological effects.[4] Pharmacokinetic interactions can result in changes in serum drug concentrations that can alter the clinical response. The most frequent pharmacokinetic drug-drug interactions involve several isoenzymes of the hepatic cytochrome P450 (CYP) and drug transporters such as P-glycoprotein and organic anion transporters.[6]

Pharmacokinetic interactions have been studied more extensively, and in-vitro and in-vivo studies indicate that changes in drug concentrations by co-administered herbs may be associated with induction or inhibition of hepatic and intestinal drug-metabolizing enzymes, especially Cytochrome P-450 (CYP), and/or drug transporters such as P-glycoprotein. Many botanicals (e.g., St. John's wort) and natural compounds isolated from plants (e.g., flavonoids, coumarins, furanocoumarins, anthraquinones, caffeine, and terpenes) have been identified as substrate inhibitors or inducers of various CYP enzymes.[6]

Interactions between herbal and synthetic drugs occur daily in patients who need long-term and continuous treatment. One of them is on sufferers of Diabetes Mellitus (DM). In DM disease, antihyperglycemic treatment is only successful in 40% of 100 people due to patient non-compliance in modifying lifestyles such as maintaining a healthy diet and increasing physical activity. In addition to the problem of non-adherence in treating ADD (Antidiabetic Drugs), DM sufferers may also use herbs that have been used empirically as drugs for DM. The use of these herbs is used as an addi-

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tional alternative treatment that is easily accessible together with ADD. This condition is based on the public's general knowledge that plants are an appropriate alternative treatment because they are believed to have no side effects and have been used for generations. Antidiabetic plants have active compounds with pharmacological effects, namely complex carbohydrates, alkaloids, glycopeptides, terpenoids, peptides, amines, steroids, flavonoids, lipids, coumarins, inorganic ions, sulfur derivatives, and other main compounds.[5]

Interactions between drugs and herbs can be seen in Table 1.

DISCUSSION

Interaction between herbs and synthetic drugs is usually haven in the pharmacokinetic and pharmacodynamic phases. The pharmacokinetic phase covers adsorption, distribution, metabolism, and excretion.[9] Pharmacokinetics An example of the pharmacokinetic interaction of herbal medicines with synthetic drugs plants Grep ran, which has interactions with several anti-epileptic, antihypertensive, and antilipidemic drugs which causes increased serum doses of these drugs and creates drug toxicity.[10] *Piper nigra* is found to increase the bioavailability of rats' rifampicin.[7] Peppermint oil capsules increased the bioavailability of felodipine, a peppermint oil inhibitor of calcium-channel blockers metabolism. An antacid could damage the enteric coating of the peppermint oil capsule.[8] Peppermint tea inhibited up to 40% of cytochrome P450 activity in an animal study after four weeks of supplementation. In an in vitro study, 20 - 500 µg/mL of peppermint oil moderately inhibited cytochrome P450 activity, and some of its isoenzymes CYPEC8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 and increase the bioavailability of drugs metabolized by them.[7,8]

Another example of the interaction of herbs with a synthetic drug was the interaction of turmeric with tacrolimus, resulting in acute calcineurin inhibitor nephrotoxicity. Tacrolimus is metabolism by cytochrome P450 (CYP) 3A enzymes, and in previous studies, turmeric has been shown to inhibit CYP3A producing a similar degree of inhibition to grapefruit juice.[4]

The interaction between parsley and paracetamol was based on experimental evidence in a small and preliminary study. In comparison, a preclinical animal study demonstrated that parsley extracts mixed with water and olive oil in a ratio of 4:3:3, which was given 2 hours before a single dose of paracetamol (80mg/kg) was found to potentiate and prolong the drug's analgesic action.[8]

Pharmacokinetic interactions between Metformin and *Aloe vera* cause decreased metformin dissolution, Metformin with *Andrographic paniculata* causes a decrease in the bioavailability of metformin, and Metformin with *Gymnema sylvestre* resulting in the achievement of maximal concentrations and slower distribution of metformin in plasma. The potential for antagonistic pharmacodynamic interactions in several studies has emerged in Metformin with *Andrographis paniculata* and *Gymnema sylvestre*. The theoretically predicted potential antagonistic interaction is Repaglinid with *Panax ginseng*. Synergistic interactions result in Metformin with *Aloe vera, Momordica charantia, Cinnamomum verum, Trigonella foenum graecum, Allium sativum,*

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Moringa oleifera, Glibenclamide with *Allium sativum*, *Cinnamomum cassia, Aloe vera*, and *Coccinia indica*. Theoretically predicted potential synergistic interactions include Glibenclamide with *Andrographis paniculata* and Pioglitazone with *Aloe vera*.[5]

Patients taking drugs with a narrow treatment window (e.g., digoxin, warfarin, immunesuppressant drugs, some antiretroviral drugs, theophylline, phenytoin, and phenobarbital) are at greater risk because relatively small changes in blood levels of these drugs can cause toxic effects or therapy failure. Furthermore, specific circumstances and conditions require that patients be regularly monitored when they are taking herbal medicines along with prescribed medicines.[11]

In addition to DM sufferers and patients with a narrow therapeutic window, antihyperlipidemic drug users must also pay attention to interactions between herbal and synthetic drugs. Many herbal medicines commonly used as antihyperlipidemic agents can interact with various synthetic drugs. In this regard, the most commonly reported herbal drug reactions are related to anticoagulant, antidepressant, antiepileptic, anti-inflammatory, and/or even antihypertensive and antilipidemic drugs.[11,12] Therefore, most of the recommended precautions are to carefully pay attention to using antilipidemic herbal medicines and other drugs and consider their synergistic effects. As previously mentioned, the most common herbal drug reactions reported occurred when taken with anticoagulant drugs. In theory, the anticoagulant effect will be increased when warfarin is combined with herbs that contain coumarins, such as boldo, fenugreek, and don quai, or combined with herbs that are antiplatelet such as danshen, garlic, and ginkgo.[12,13] Two case reports demonstrated that patients on therapy with warfarin experienced severe spontaneous bleeding after taking ginkgo independently.[14,15] In addition to causing spontaneous bleeding, ginkgo was also found to increase blood pressure in elderly patients prescribed thiazide diuretics to treat hypertension.[16] This is because ginkgo has properties as a peripheral vasodilator. [14,15]

Avocados may interact with warfarin and MAO inhibitors. Pomegranate interacts with antihypertensive and antilipidemic drugs, which cause potentiation and increase the risk of rhabdomyolysis. Bilberries may interact with Aspirin, NSAIDs, Insulin, and anticoagulants, causing an increased risk of bleeding.[10] The main interactions of ginger with synthetic drugs are generally related to antidepressants, antiarrhythmic drugs, and anticoagulants. Green tea may also interact with adenosine, antiandrogens, theophylline, and anticoagulants.[10] Grapes only interact with methotrexate resulting in increased side effects of this drug. Psyllium often interacts with anticoagulants, antidepressants, digoxin, carbamazepine, lithium, and some diuretics, so simultaneously using these two drugs is not recommended. Oil evening primros *e*may interact with various drugs such as analgesics, antiepileptic drugs, MAO inhibitors, antipsychotic drugs, and even statins. Celery often interacts with ACE inhibitors, alcohol, and anticoagulants. The main interactions between Row Yar and other drugs are defined for drugs used in the treatment of photodermatitis that cause increased photosensitivity.[10] Use of Dandelion may cause interactions with metronidazole. The use of Cabbage can also interact with acetaminophen and

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vitamin K antagonists. Ginko biloba mainly interacts with anticoagulants, antiepileptic drugs, MAO inhibitors, and antidepressants. Ginseng can also interact with antihypertensive drugs, digoxin, steroid drugs, immunosuppressive drugs, and hypnotics.[10]

Some antilipidemic drugs of plant origin can also be accompanied by severe metabolic disturbances and complications during pregnancy and lactation, so their administration should be carried out with full knowledge of their side effects. Some herbal remedies include avocado, bilberry, ginger, green tea, psyllium, saffron, celery, and Cabbage, which should be used with caution in patients with coagulation disorders, as well as in those with a history of cardiovascular and/or cerebrovascular disorders.[10]

Assessment of the risks associated with herbal drug interactions should consider several factors. One such factor is the quality of evidence provided for herbal drug interactions. For example, the results obtained from an in vitro trial may only indicate a potential interaction, whereas a clinical trial is placebo-controlled, double-blind with clinically relevant endpoints, and can be considered highly accurate. Aspects of the quality of herbal medicines that cause interactions must be considered, which include factors such as counterfeiting, proper identification and origin of the plant, dosage, and phytochemical composition. Other factors include the severity of side effects and/or toxic effects, duration of symptoms if treatment failure occurs due to herbal drug interactions, and frequency of occurrence (e.g., number of case reports). Furthermore, pharmacokinetic drug-herb interactions should be evaluated on the same principles as drug-drug interactions, such as determining the no-effect limit based on the maximum tolerated dose.[11] Furthermore, statistically significant changes in plasma drug levels by herbal medicines can occur without clinically significant effects. Herbal drug interactions can be avoided or managed by giving patients the correct advice based on reliable information. Educating and making healthcare providers aware of the dangers associated with herbal drug interactions through accurate resources and publications based on scientific studies can contribute to managing the situation and thereby reducing harmful and detrimental effects.[11]

Thus, the main basic principle of administering these medicines includes full awareness of the doctor about the effects and interactions between herbal medicines with herbal medicines and herbal medicines with synthetic drugs. Health workers are also expected to educate people not to arbitrarily use herbal or synthetic medicines and strictly monitor the community's verification and distribution of medicines. In addition, it is also recommended that a doctor is consulted before integrating herbal remedies into daily regimens.[10]

CONCLUSION

Traditional medicine is an ingredient derived from plants, animals, minerals, or a mixture of these materials, which is usually used for generations for treatment, disease prevention, and health maintenance. In the beginning, the principles of conventional medicine were intensively developed. However, due to reports of high side effects associated with these biosynthetic drugs, public attention has recently become more open to using herbs as a substitute

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for biosynthetic drugs to prevent the side effects of synthetic drugs. Interactions are said to occur when the presence of another drug, food, or drink changes the effect of one drug. Herbal medicines follow modern pharmacological principles. Therefore, herb-drug interactions can be characterized by either pharmacokinetic or pharmacodynamic mechanisms. The main basic principles for administering these medicines include the doctor's full awareness of the effects and interactions between herbal and herbal medicines and herbal and synthetic drugs. Health workers are also expected to educate people not to arbitrarily use herbal or synthetic medicines and strictly monitor the community's verification and distribution of medicines.

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