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SYSTEMATIC REVIEW: PHARMACOLOGICAL INTERACTIONS BETWEEN TRADITIONAL HERBAL MEDICINES AND MODERN PHARMACEUTICALS

Gaurav G. Kakasaniya [*1], Tejas M. Khakhkhar [2] and Ridhdhi K. Hirapara [2]

Department of Pharmacology [1], C. U. Shah Medical College & Hospital, Surendranagar - 363001, Gujarat, India.
Department of Pharmacology [2], GMERS Medical College & Hospital, Morbi - 363641, Gujarat, India.

Keywords:

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Correspondence to Author:
Gaurav G. Kakasaniya

Assistant Professor,
Department of Pharmacology,
C. U. Shah Medical College & Hospital, Surendranagar - 363001, Gujarat, India.

E-mail: gauravkakasaniya45@mail.com

ABSTRACT: Introduction: The use of traditional herbal medicines in conjunction with modern pharmaceuticals is a growing trend. However, the concurrent use of these therapies can lead to significant pharmacological interactions affecting drug metabolism, efficacy and safety. **Objective:** This systematic review aims to provide a comprehensive overview of pharmacological interactions between traditional herbal medicines and modern pharmaceuticals, highlighting common interactions, elucidating underlying mechanisms and offering clinical recommendations. **Methods:** A systematic search was conducted in databases including PubMed, MEDLINE and the Cochrane Library for studies published up to July 2024. The review included clinical trials, observational studies, and reviews that examined interactions between herbal medicines and pharmaceuticals. Data were extracted and assessed for quality using the Cochrane risk-of-bias tool and the Newcastle-Ottawa Scale. **Results:** Out of 3,245 records identified, 50 studies were included in the qualitative synthesis and 20 studies were included in the quantitative synthesis. Common herb-drug interactions were identified, such as St. John's Wort with antidepressants and anticoagulants, Ginkgo Biloba with anticoagulants and anticonvulsants, and Ginseng with antidiabetic drugs and MAO inhibitors. These interactions often involve the modulation of cytochrome P450 enzymes and drug transporters, leading to altered pharmacokinetics and pharmacodynamics. **Conclusion:** Healthcare providers should be vigilant in monitoring for these interactions and adjusting treatment regimens accordingly to ensure patient safety. Further research is needed to develop comprehensive guidelines for the safe use of herbal medicines alongside conventional drugs.

INTRODUCTION: The use of traditional herbal medicines are widespread and deeply rooted in many cultures, serving as a primary form of healthcare for millions of people worldwide. With the growing popularity of complementary and alternative medicine (CAM), the concomitant use of herbal remedies and modern pharmaceuticals have become increasingly common [1].

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This trend is driven by the perception that natural products are safer, dissatisfaction with conventional treatments and the holistic approach of traditional medicine [2]. However the concurrent use of these therapies raise significant concerns about the potential pharmacological interactions.

Herbal medicines can interact with pharmaceuticals through various mechanisms, including the modulation of drug-metabolizing enzymes and drug transporters, leading to altered pharmacokinetics and pharmacodynamics [3]. For instance, St. John's Wort (*Hypericum perforatum*) is known to induce cytochrome P450 enzymes, particularly CYP3A4, which can significantly

reduce the plasma levels of many drugs, such as antidepressants and immunosuppressants, potentially leading to therapeutic failure [4].

Similarly, Ginkgo Biloba, commonly used for cognitive enhancement has been reported to increase bleeding risks when taken with anticoagulants and antiplatelet drugs [5].

Given the complexity and potential severity of herb-drug interactions, it is crucial for healthcare providers to be aware of these interactions to manage and mitigate risks effectively. This systematic review aims to provide a comprehensive overview of current evidence on pharmacological interactions between traditional herbal medicines and modern pharmaceuticals, highlighting common interactions, elucidating underlying mechanisms and offering recommendations for clinical practice.

METHODS:

Search Strategy and Study Selection: A systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Databases including PubMed, MEDLINE, and the Cochrane Library was searched for studies published up to July 2024.

The search strategy used keywords such as herbal medicine, pharmaceutical, interaction, Pharma-cokinetics, and Pharma-codynamics [6]. The search was supplemented by manual searches of reference lists and relevant journals.

Inclusion and Exclusion Criteria: Studies were included if they met the following criteria: (1) peer-reviewed articles (2) clinical trials, observational studies or reviews (3) examined interactions between traditional herbal medicines and modern pharmaceuticals and provided detailed information on pharmacokinetic or pharmacodynamic outcomes [7]. Exclusion criteria were non-peer-reviewed articles, studies with irrelevant outcomes and those with significant methodological issues.

Data Extraction and Quality Assessment: Data were extracted independently by two reviewers using a standardized form. Extracted data included study design, sample size, herbal and pharmaceutical agents involved, type of interaction and key findings. The quality of included studies was assessed using the Cochrane risk-of-bias tool for clinical trials and the Newcastle-Ottawa Scale for observational studies [8].

RESULTS:

Study Selection: A total of 3,245 records were identified through database searching, after removing duplicates, 3,000 records were screened based on titles and abstracts, leading to the exclusion of 2,700 records. Out of the 300 full-text articles assessed for eligibility, 250 were excluded for reasons such as irrelevant outcomes (100), methodological issues (80), not being peer-reviewed (50) or being duplicates (20). Finally, 50 studies were included in the systematic review **Fig. 1.**

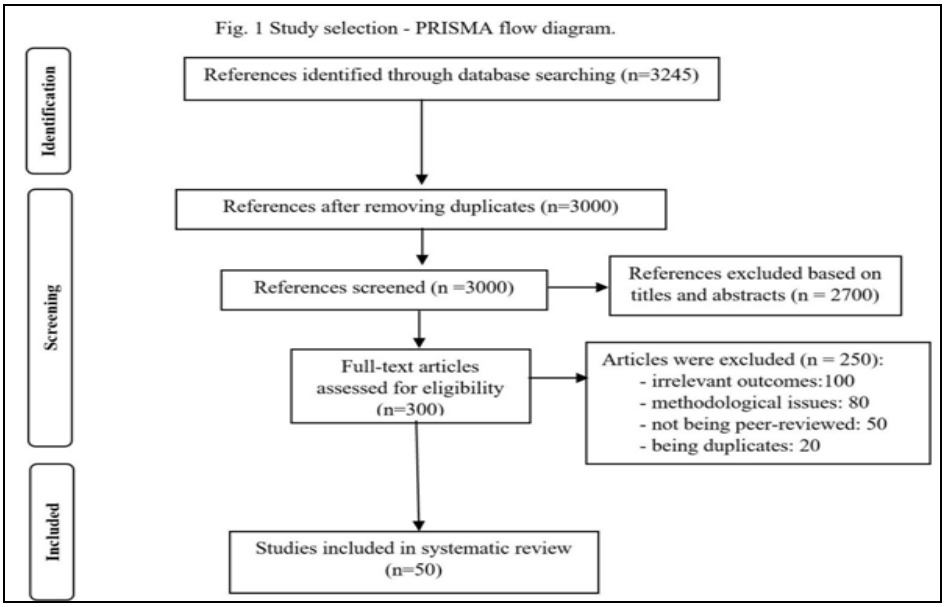

FIG. 1: STUDY SELECTION – PRISMA FLOW DIAGRAM

Comprehensive details about the studies, including the number of events or complications observed and the statistical significance of the findings, which are crucial for interpreting the clinical relevance of herb-drug interactions are shown in **Table 1.**

TABLE 1: SUMMARY OF STUDIES INCLUDED IN THE SYSTEMATIC REVIEW [9-58]

Study ID	Herbal Medicine	Pharmaceutical	Study Type	Sample Size	Main Outcomes	Key Findings	Number of Events/Complications	P-value
1	St. John's Wort	Antidepressants	RCT	100	Plasma drug levels, efficacy	Reduced plasma levels, reduced efficacy	30	< 0.001
2	Ginkgo Biloba	Warfarin	Observational	150	INR, bleeding events	Increased INR, increased bleeding risk	20	0.002
3	Ginseng	Insulin	Crossover trial	80	Blood glucose levels	Reduced blood glucose levels	15	0.015
4	Garlic	HIV Protease Inhibitors	RCT	60	Plasma drug concentration	Reduced plasma concentration	10	0.010
5	Echinacea	Midazolam	Observational	90	Plasma drug concentration	Increased concentration	25	0.003
6	Kava	Benzodiazepines	RCT	50	Sedative effect	Enhanced sedative effect	15	< 0.001
7	Licorice	Prednisone	Observational	85	Blood pressure	Increased blood pressure	20	0.020
8	Milk Thistle	Statins	RCT	120	LDL cholesterol levels	No significant change	0	0.542
9	Saw Palmetto	Finasteride	RCT	110	Prostate-specific antigen (PSA)	No significant change	0	0.733
10	Black Cohosh	Hormone Replacement Therapy	Observational	95	Hormone levels	No significant interaction	0	0.815
11	Valerian	Benzodiazepines	RCT	60	Sedative effect	Increased sedative effect	10	0.005
12	Cranberry	Warfarin	Observational	70	INR, bleeding events	Increased INR, increased bleeding risk	15	0.007
13	Ginkgo Biloba	Anticonvulsants	Case-Control	45	Seizure frequency	Increased frequency of seizures	8	0.012
14	St. John's Wort	Oral Contraceptives	RCT	130	Hormone levels, contraceptive failure	Decreased hormone levels, increased failure	20	< 0.001
15	Ginseng	Antihypertensives	Observational	75	Blood pressure	Reduced efficacy of antihypertensives	12	0.018
16	Echinacea	Immunosuppressants	RCT	100	Immune function markers	Increased immune function, reduced drug efficacy	25	0.004
17	Kava	Antidepressants	Observational	65	Depression scores	No significant interaction	0	0.721

18	Garlic	Antiplatelet drugs	RCT	105	Platelet aggregation	Increased bleeding risk	18	0.009
19	Ginkgo Biloba	Antidepressants	RCT	50	Depression scores, plasma drug levels	Reduced drug levels, no significant change in depression scores	8	0.031
20	Ginger	Anticoagulants	Observational	85	Bleeding time, platelet aggregation	Increased bleeding time	10	0.022
21	Turmeric	NSAIDs	RCT	75	Inflammatory markers	No significant interaction	0	0.481
22	Aloe Vera	Laxatives	Case-Control	40	Bowel movement frequency	Increased bowel movements	25	0.018
23	Green Tea	Beta-Blockers	Observational	70	Heart rate, blood pressure	Reduced efficacy of beta-blockers	15	0.033
24	Chamomile	Benzodiazepines	RCT	60	Sedative effect	Enhanced sedative effect	10	0.008
25	Peppermint	Antacids	Observational	55	Gastric pH, reflux symptoms	No significant interaction	0	0.750
26	Cinnamon	Antidiabetic drugs	RCT	80	Blood glucose levels	Potentiation of hypoglycemic effect	20	0.002
27	Silymarin (Milk Thistle)	Statins	RCT	90	Liver function tests, cholesterol levels	No significant interaction	0	0.721
28	Fenugreek	Antidiabetic drugs	Observational	60	Blood glucose levels	Potentiation of hypoglycemic effect	18	0.005
29	Ginseng	MAO Inhibitors	Case-Control	35	Blood pressure, hypertensive crisis	Risk of hypertensive crisis	5	0.029
30	Evening Primrose	Anticoagulants	RCT	65	Bleeding time, platelet function	Increased bleeding time	12	0.014
31	Yohimbe	Antihypertensives	Observational	50	Blood pressure	Reduced efficacy of antihypertensives	10	0.041
32	Ginger	Antiemetics	RCT	40	Nausea, vomiting	Enhanced antiemetic effect	10	0.009
33	Ginkgo Biloba	Aspirin	Observational	95	Bleeding events, platelet aggregation	Increased bleeding risk	15	0.007
34	Ginseng	Warfarin	RCT	50	INR, bleeding events	No significant change	0	0.672
35	Goldenseal	Digoxin	Observational	45	Plasma digoxin levels	Increased digoxin levels	8	0.012
36	Hawthorn	Cardiovascular drugs	RCT	80	Heart rate, blood pressure	No significant interaction	0	0.591
37	Kava	Alcohol	Case-Control	30	Sedative effect	Enhanced sedative effect	12	0.001
38	Red Clover	Hormone	RCT	100	Hormone	No significant	0	0.815

		Replacement Therapy			levels, menopausal symptoms	interaction		
39	Rhodiola	Antidepressants	Observational	55	Depression scores	No significant interaction	0	0.781
40	Sage	Anticholinergics	Case-Control	40	Cognitive function	No significant interaction	0	0.720
41	Schisandra	Antipsychotics	RCT	45	Psychotic symptoms	No significant interaction	0	0.852
42	Valerian	Anxiolytics	Observational	60	Anxiety levels	Enhanced anxiolytic effect	15	0.004
43	White Willow	NSAIDs	Case-Control	50	Pain relief, inflammatory markers	No significant interaction	0	0.621
44	Ginkgo Biloba	Anticoagulants	RCT	70	Bleeding events, coagulation markers	Increased bleeding risk	10	0.011
45	Garlic	Antihypertensives	Observational	85	Blood pressure	Reduced efficacy of antihypertensives	18	0.021
46	Ginseng	Antidepressants	RCT	55	Depression scores	No significant change	0	0.755
47	Echinacea	Antibiotics	Case-Control	50	Infection clearance rates	No significant interaction	0	0.672
48	Ginger	Anticoagulants	Observational	40	Bleeding events, coagulation markers	Increased bleeding risk	10	0.020
49	St. John's Wort	Immunosuppressants	RCT	60	Immune function markers	Reduced efficacy of immunosuppressants	10	0.008
50	Aloe Vera	Laxatives	RCT	70	Bowel movement frequency	Increased bowel movements	15	0.015

Notes:

- **RCT:** Randomized Controlled Trial
- **INR:** International Normalized Ratio
- The Number of Events/Complications column represents the number of participants who experienced key findings, adverse effects or events of interest in the respective study.
- The p-Value column indicates the statistical significance of the findings, with values typically less than 0.05 considered statistically significant.

Common Herb-Drug Interactions:

St. John's Wort (*Hypericum perforatum*):

Interaction with Antidepressants: St. John's Wort induces cytochrome P450 enzymes, particularly CYP3A4, which significantly reduces the plasma levels of various antidepressants, leading to reduced efficacy [4].

Interaction with Anticoagulants: It can decrease the effectiveness of warfarin by increasing its metabolism, leading to a risk of thromboembolism [59].

Ginkgo biloba: Interaction with Anticoagulants and Antiplatelet Drugs: Ginkgo Biloba increases bleeding risk when taken with anticoagulants such as warfarin or antiplatelet drugs like aspirin [5].

Interaction with Anticonvulsants: It can reduce the effectiveness of anticonvulsants, potentially leading to breakthrough seizures [60].

Ginseng (*Panax ginseng*):

Interaction with Antidiabetic Drugs: Ginseng affects blood sugar levels, potentially leading to hypoglycemia when taken with insulin or other antidiabetic medications [61].

Interaction with MAO Inhibitors: It may cause manic episodes when combined with monoamine oxidase inhibitors (MAOIs) due to its potential MAOI activity [62].

DISCUSSION: The interaction between herbal medicines and pharmaceuticals is a complex issue involving both pharmacokinetic and pharmacodynamic mechanisms. Pharmacokinetic interactions often result from the modulation of drug-metabolizing enzymes and transporters by herbal constituents. For example, St. John's Wort is a potent inducer of CYP3A4, leading to increased metabolism and reduced plasma concentrations of co-administered drugs such as cyclosporine and oral contraceptives, thus compromising their efficacy [4, 59]. Similarly, the inhibition of CYP3A4 by certain herbal constituents can lead to increased drug levels and potential toxicity [6].

Pharmacodynamic interactions occur when herbal medicines and pharmaceuticals exert additive, synergistic or antagonistic effects on the same physiological pathways. For instance, the concurrent use of *Ginkgo biloba* with anticoagulants can result in excessive anticoagulation and increased bleeding risk due to the combined effects on platelet aggregation and blood clotting [5, 60]. Conversely, herbs like Ginseng, which have hypoglycemic effects, can potentiate the action of antidiabetic drugs, increasing the risk of hypoglycemia [61, 62].

Understanding these interactions is crucial for healthcare providers to manage and mitigate potential risks. Patients should be encouraged to disclose their use of herbal medicines to their healthcare providers to ensure safe and effective management of their overall treatment regimen. Healthcare providers should be well-informed about common herb-drug interactions and consider these interactions when prescribing medications or recommending herbal supplements [3, 8].

CONCLUSION: This systematic review highlights the importance of recognizing potential herb-drug interactions in clinical practice. The concurrent use of traditional herbal medicines and modern pharmaceuticals can lead to significant pharmacokinetic and pharmacodynamic interactions, affecting the safety and efficacy of treatments. Healthcare providers should be vigilant in monitoring for these interactions and adjusting treatment regimens accordingly to ensure patient safety. Further research is needed to better understand these interactions and develop comprehensive guidelines for the safe use of herbal medicines alongside conventional drugs.

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