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HERB DRUG INTERACTIONS: CHALLENGES FOR CANCER PATIENTS UNDERGOING CHEMOTHERAPY

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Abstract
Almost all societies have utilized medicinal herbs as a source of treatment. For thousands of years, people have utilized medicinal herbs to cure illnesses, preserve food, and enhance its flavor. Over the ages, human groups have shared knowledge of their therapeutic qualities with one another. Although modern scientific medicine has made great strides, traditional medicine remains the primary means of treating diseases for the majority of people in developing countries, including India. Even among those who have access to western medicine, the number of people using complementary and alternative medicine is still high. Active compounds produced during secondary metabolism are typically responsible for the biological properties of plant species used throughout the globe for various purposes, including treatment of chronic diseases. According to epidemiological data, nutrition has a significant impact on both human health and the management of a number of chronic illnesses, such as cancer. Certain medicinal herbs have antitumor chemicals, which make them potential candidates for chemotherapy preventive agents against the development of cancer. However, on occasion, these agents may react with the active ingredient and alter the therapeutic property's potency. In this study, an attempt has been made to draw attention to the possible interactions between the active substances and herbal components.

Keywords- Cancer, anticancer agents, complementary medicines, therapeutic activity

Introduction to herbal medicines

Herbal market in India comprises a major share of all officially recognized health systems. It is increasing date by day rapidly and has grown to multi-billion rupees industry. All age group of Indian populations are attracted to the growing influencing market and are using these drugs without the knowledge of the physicians [1]. Majority of populations in India approximately 70% use non-allopathic medications. The use of these complementary and alternative medicines (CAM) is mounting very fast in current scenario. The National Center for Complementary and Herbal Medicines defines CAM 'as a group of diverse medical and health care systems and products that are not included as a part of conventional medicine system'. CAM are the substances which are biologically obtained from natural sources like herbs, vitamins and foods. The pharmacodynamic and pharmacokinetic properties of these herbal drugs are of utmost importance as they can interfere with the allopathic medications consumed by people [2]. Majority of patients are moving towards the use of these herbal drugs with concomitant use of allopathic system of medicines. Factors contributing to this practice are dissatisfaction of allopathic therapies; patient's own belief system in

alternative herbal practice, patient's psychology. Generally patients are unintentionally combining the use of these CAM with prescribed allopathic medicines without taking opinion with the physicians for concomitant use. Physicians also do not take interest in counselling the patients regarding their any alternative therapy during treatment [3]. The major concern is that consuming these herbs can interact with prescribed drugs used by the patients. It is of utmost importance that clinicians should understand the potential herb drug interactions in patients to overcome serious fatal side-effects. There are many complex pharmacological activities of such herbal medicines, which have not been identified yet. The selection criteria of this review forced the author to review the existing data about various herbs used by anticancer patients during chemotherapy treatment and potential herb- drug interactions, which interfered with their treatment duration.

1. Complementary and alternative medicines use in various diseases

Based upon several clinical findings it is a proven fact that herbal supplements are used by Indian populations in many diseases.

2.1. Cancer-

Worldwide incidences of cancer patients are increasing due to variation in lifestyle, genetic factors and other chemical/environmental factors. These changes forced patients for co-administration of these herbal medicines along with their conventional allopathic chemotherapeutic agents. Various herbs such as St. John's wort, grapefruit juice, ginseng, Echinacea, garlic, etc. are used with a belief that they will kill or suppress the growth of uncontrolled tumour cells, improving cancer-related symptoms and severe side effects of chemotherapy and ultimately reducing the duration of cancer treatment. These herbs contain many phytoconstituents which can interact with various enzymes, transporters and DNA, which will reduce the therapeutic index of anticancer drugs.

Table 1 List of herbal drugs that possess anticancer activity-

S.NO	HERBAL DRUGS	INGREDIENTS	REFERENCES
1.	Podophyllum peltatum (American May Apple) and Podophyllum hexandrum (Himalayan May Apple).	Podophyllin, astragalin	[3]
2.	Taxus brevifolia (Pacific Yew Tree)	Taxanes, taxol cepholomannine	[3]
3.	Allium sativum (Garlic)	Alliin, allicin alliin, alliinase	[5,6]
4.	Gyrophora esculenta (Maitake)	Polysaccharides β-glucans, α-glucans	[7]
5.	Aconite	Aconitine, hypaconitine, neopelline, napelline, neoline	[9]
6.	Bromelain		[11]
7.	Curcuma longa (Turmeric)	Curcuminoids, curcumin, volatile oil, starch	[12]
8.	Betula utilis (White-barked Birch Tree)	betulinic acid	[9]
9.	Silybum marianum (Milk thistle)	silymarin and silybin	[10]
10.	Echinacea angustifolia	Arabinogalactan	[11]
11.	Uncaria tomentosa (Cat's claw)	polyphenols, triterpines, campesterol, stigmasterol and beta-sitosterol.	[12]
12.	Camellia sinensis (Green tea)	Epigallocatechin gallate	[9]
13.	Aloe vera	Aloe-emodin, emodin, aloin	[9]
14.	Chlorella pyrenoidosa	Lysine	[15]
15.	Withania somnifera	Withanolides, Withaferin	[16]
16.	Camptothecin	18-OH-camptothecin, 11-OH-camptothecin	[19]
17.	Ellipticine	9-methoxy ellipticine	[12]
18.	Actinidia chinensis (Yang-t'ao)	Polysaccharide known as "ACPS-R"	[14]

19.	Gossypium barbadense	Gossypol	[19]
20.	Combretum caffrum (African Willow Tree)	Combretastatin	[12]
21.	Panax ginseng (Ren-Shen/Ginseng)	Ginsenosides, Panaxosides	[18]
22.	Ginkgo biloba (Yin Guo/ Bai Guo)	Ginkgolide-B, A, C and J	[16]
23.	Angelica sinensis (Dang Gui)	Polysaccharide fraction "AR-4"	[17]
24.	Catharanthus roseus or Vinca rosea (Periwinkle)	Vinblastine, Vincristine	[19]
25.	Lentinus edodes	Lentinan	[19]
26.	Glycine max	Zinc, selenium, vitamins (A, B1, B2, B12, C, D, E and K),	[20]
27.	Ochrosia elliptica	Ellipticine and 9-methoxy ellipticine	[21]
28.	Aglaila sylvestre	Silvesterol	[22]
29.	Viola odorata	Essential oil, alkaloid, saponins, glycoside of methyl salicylate.	[20]
30.	Linum usitatissimum	Cynogenetic glycosides, Lignans	[21]
31.	Mentha species	Bromelain	[22]
32.	Ananas comosus	Polysaccharide fraction "AR-4"	[22]
33.	Angelica sinensis	Acetogenins	[22]
34.	Annona species	Potent anticancer factors	[22]
35.	Arctium lappa	Swainsonine	[22]
36.	**Astragalus membranaceus**		**[16]**

2.2.1Cardiovascular disorders-
Global incidence of disorder relating cardiovascular system is increasing rapidly. Herbs such as ginkgo, fenugreek, garlic and other coumarin derivatives caused synergistic activity with other antiplatelet drugs (warfarin). Warfarin acts by antagonizing the pathway of vitamin-K mediated synthesis of blood clotting factors. Anticoagulant property was increased when warfarin was co-administered with fenugreek, garlic. Whereas EGCG an active constituent of green tea antagonizes the anti coagulant activity of warfarin [6].

2.3 Psychological disorders
Psychological disorders include depression, psychosis, mania, Alzheimer and anxiety. Depression is a unipolar disorder in which serotonin (5 hydroxy tryptamine) concentration in post synaptic terminal decreases. St. John's wort a well-known herb is widely used in treating depression relating symptoms. It is proven that it inhibits the reuptake of serotonin from axonal membrane of neurons [7]. Therefore, St. John's wort and antidepressants concomitant use have been seen widely. Prolonged use of this herb interacts with serotonin reuptake inhibitors (fluoxetine, fluvoxamine, paroxitine) and produces maniac episodes. Other herbs that interact with antidepressants are ginkgo and ginseng. The number of cancer patients worldwide is rising as a result of varying lifestyles, genetics, and other chemical and environmental factors. These modifications required patients to take these herbal remedies in addition to their regular allopathic chemotherapy drugs [10**].**

2.3 HIV-
Patients with HIV pose a growing threat to the world's health care systems. Since there are now powerful antiviral medicines that have successfully reduced the death rate of AIDS, the number of patients dying from the disease is declining. Because of these side effects, the patient's immune response diminishes. For improved health, the patient takes immunomodulatory herbs (curcuma caesia, zingiber officinalis, allium sativum, aloe barbadensis, and moringa oleifera). The antiviral medication atazanavir interacts with these botanicals, reducing its bioavailability. Enzyme induction, the transporter efflux mechanism, and phase II reaction modulation were all engaged in

this, which ultimately led to toxicity in the human body and the failure of antiretroviral medications [11].

Herbal medicine interactions have also been demonstrated in various illnesses such as anxiety, psychosis, hepatic disorders, and other problems. Our focus is on highlighting potential mechanisms of herb-drug interactions between conventional anticancer allopathic medications and herbal medicines used in chemotherapy. An estimated 60% of patients reportedly use these supplements to expedite their recovery and get past the significant side effects of their chemotherapy programme. Despite numerous surveys, investigations, and reviews of the literature, there are still some unidentified relationships between herbal medications and cancer patients that need to be found in order to improve palliative care and expedite recovery. Additionally, this evaluation will advise doctors on how to safely combine herbal remedies with chemotherapy medications [12].

3 Use of CAM and herb drug interaction in Cancer patients

Cancer is a serious condition caused by unchecked cell growth. Patients undergoing this treatment comprise 65% of all Indians who are predominantly dependent on chemotherapy, and 70% of men and women die from cancer. Research indicates that individuals diagnosed with cancer frequently use large amounts of herbal supplements (CAM) in an attempt to expedite the healing process. Pharmacokinetic and pharmacodynamic herb-drug interactions resulted from the 1990s interactions between complementary and alternative medicine (CAM) and certain anti-cancer drugs [14]. The dynamics of medication absorption, distribution, metabolism, and elimination are disrupted by pharmacokinetic drug interactions. Drugs and substances that compete for the same biotransformation (metabolism) pathway are said to interact pharmacokinetically. The drug's plasma concentration rises when the route becomes saturated for whatever cause, making it impossible for the drug to be metabolised completely. When a drug and a substance attach to the same macromolecular target or interfere with drug binding transporters, a pharmacodynamic interaction takes place. Co-administration of these medications with substances that may cause pharmacodynamic interactions can result in synergism or an additive mechanism that can be harmful and lead to major side effects. About 70% of patients do not tell their doctors that they take complementary and alternative medicine (CAM) in addition to allopathic anticancer medications [15].

Patients mostly with breast cancer employ a variety of complementary and alternative medicine. Many oncolytic medications may have a lower therapeutic index as a result of these possible interactions. It is thought that interactions between CAM and anticancer medications significantly change pharmacokinetics, which may contribute to unanticipated toxicities and undertreatment in individuals receiving chemotherapy. The term "drug interaction" refers to a negative indication on the body of the patient that may have detrimental consequences. Drug interactions can produce a unique reaction that does not happen when either medication is given alone, as well as raise or decrease the therapeutic or unfavorable response. Numerous phyto-active plant elements found in these supplements interact with the body's pharmacologic system to potentially generate effects [16]. If pharmacological, toxicological, and clinical research is done on these herbs, along with monitoring for any potential side effects, these interactions can be managed and concurrent use of these herbal medications with traditional allopathic medications can be encouraged [17].

Table 2 List of herbs used by cancer chemotherapeutic patients who caused possible reported herb drug interactions.

S.No.	Drug	Interaction	Comments	Mechanism
1.	Irinotecan (anticancer drug)	St. John wort Ginseng	↓ SN-38 active metabolite blood level, ↓ myelo suppression May cause failure of cancer therapy	P-glycoprotein (ABCB-1, MDR-1) [17]
2.	Vinblastine	Ginseng	CYP3A4 ↓	P-

				glycoprotein (ABCB-1, MDR-1) [18]
3.	Epipodophyllotoxins, taxanes,	Garlic oil	CYP3A4 ↓	P-glycoprotein (ABCB-1, MDR-1) [19]
4.	Epipodophyllotoxins, taxanes,	Milk thistle	CYP3A4 ↓	P-glycoprotein (ABCB-1, MDR-1) [19]
5.	Camptothecins, cyclophosphamide, EGFR-TK inhibitors, epipodophyllotoxins, taxanes, and vinca discourage with alkylating agents, antitumor antibiotics, and platinum analogues (free-radical scavenging)	Ginkgo	(CYP3A4 and CYP2C19 inhibition); (free-radical scavenging)	P-glycoprotein (ABCB-1, MDR-1) [12]
6.	Camptothecins, cyclophosphamide, EGFR-TK inhibitors, epipodophyllotoxins, taxanes, and vinca alkaloids methotrexate	Echinacea	(CYP3A4 induction)	P-glycoprotein (ABCB-1, MDR-1) [12]
7.	tamoxifen, and treatment of patients with estrogen-receptor positive breast cancer and endometrial cancer	Soy	(antagonism of tumor growth inhibition) (stimulation of tumor growth)	P-glycoprotein (ABCB-1, MDR-1) [12]
8.	Cyclophosphamide	Saw palmetto	CYP3A4 inhibition	[13]
9.	Avoid with all concurrent chemotherapy	St. John's wort	(CYP2B6, CYP2C9, CYP2C19, CYP2E1, CYP3A4, and P-glycoprotein induction)	ABC, ATP-binding cassette; BCRP [14]
10.	Tamoxifen cyclophosphamide, and teniposide, cyclophosphamide, and teniposide	Valerian	(CYP2C9 inhibition), (CYP2C19 inhibition) (CYP2C19 inhibition)	ABC, ATP-binding cassette; BCRP, [17]
11.	Hepatotoxic chemotherapy; caution with camptothecins, cyclophosphamide, EGFR-TK inhibitors, epipodophyllotoxins, taxanes, and vinca alkaloids	Kava	(CYP3A4 induction)	MRP-1 (ABCC-1)[16]
12.	Camptothecins, cyclophosphamide, EGFR-TK inhibitors, epipodophyllotoxins, taxanes, and vinca alkaloids, and with alkylating agents, antitumor antibiotics, and platinum	Grape seed	(CYP3A4 induction) (free-radical scavenging)	MRP-1 (ABCC-1) [17]

	analogues			
13.	Epipodophyllotoxins, taxanes,	β-carotene	↑ CAT activity ↑ CYP3A4/3A5, MDR-1, and MRP-2	[18]
14.	Epipodophyllotoxins, taxanes,	Apo-carotenals	↑ CAT activity	[18]
15.	Epipodophyllotoxins, taxanes,	Quercetin	↑ CYP3A4 mRNA	[18]
16.	Epipodophyllotoxins, taxanes,	Retinol	↑ CAT activity ↑ CYP3A4/3A5, MDR-1, and MRP-2	[18]
17.	Epipodophyllotoxins, taxanes,	Vitamin E	↑ CAT activity for α and γ Effective binding to PXR ↑ CYP3A4, no effect on UGT1A1 or MDR-1 ↑ MDR-1, ↑ UGT1A1, no effect on CYP3A4 ↑ CYP3A4/3A5 by γ	[18]
16.	Epipodophyllotoxins, taxanes,	Black pepper	Inhibitor of CYP3A4, PgP	[19]
17.	Epipodophyllotoxins, taxanes,	Seville orange	Inhibitor of CYP3A4	[22]

Patients with cancer may experience major safety concerns if they utilise these alternative medications for an extended period of time. It is crucial to comprehend the various mechanisms underlying herb-drug interactions in order to streamline this strategy. The therapeutic efficacy of anticancer medications may be compromised by a pharmacokinetic interaction. The stimulation of metabolising enzymes (Cytochrome P450), drug transporters (P-glycoprotein), and other metabolic pathways, If cancer patients use these alternative treatments over an extended period of time, there may be serious safety risks. To make this method more efficient, it is essential to understand the different mechanisms that underlie herb-drug interactions. A pharmacokinetic interaction may impair the anticancer medication's therapeutic efficacy. Almost all pharmacokinetic interactions involve the activation of drug transporters (P-glycoprotein), metabolising enzymes (Cytochrome P450), and other metabolic pathways. Many chemotherapy drugs pass through Phase I (oxidation-CYP3A4 mediated hydroxylation) and Phase II (glucoronide conjugation) processes in the metabolic route.

P-glycoprotein, other cytochromes, uridine diphosphoglucuronosyl transferase (UGT), and CYP3A4 substrates can all be stimulated or inhibited by herbs.St. John's wort (SJW) is one herb-drug interaction that significantly affects the pharmacokinetics of chemotherapeutic medications. The stimulation of drug metabolism-related enzymes was one of the noted possible side effects [14]. This can reduce the plasma concentration of anticancer drugs and result in treatment failure. Patients with cancer who used SJW in addition to irinotecan had plasma levels of SN-38, the active metabolite of irinotecan, 42% lower [4]. Rats given 14 days of SJW exposure demonstrated a comparable impact, with both SN-38 and irinotecan's maximum measured concentrations (Cmax) significantly declining [5].

Patients should be advised not to use SJW because of the marked drop in SN-38 plasma levels in order to prevent under treatment [14]. The same advice may be given to patients receiving treatment with the protein-tyrosine kinase inhibitor imatinib. In healthy individuals, imatinib with SJW led to a 43% increase in imatinib clearance. A t1/2 half-life, a significant drop in Cmax, and a 32% decrease in the mean area under the concentration–time curve (AUC) were also observed. Although this may seem like a minor consequence, imatinib plasma concentrations may drop below the minimal effective amount following the recommended 400 mg dose. Those who take multiple medicines are more likely to develop herb-drug interactions due to polypharmacy and self-medication [17].

4 Mechanism of herb-drug interaction

Herbal supplements may not work as intended due to toxicity, adverse effects, or diminished medicine exposure to various drug receptors. They may also alter the active ingredients (drug's)

systemic concentration [6]. It is believed that both biological and physicochemical processes produce these effects. Research on the pharmacokinetic and pharmacodynamic pathways resulting from herb-drug interactions is necessary to establish the optimal course of interactions. Physicians benefit from treatment and knowledge about preventing drug interactions. Factors such as inter-individual situations, co-morbid diseases, sex, age, and body size can affect these types of relationships. Cell DNA, cell membrane transporters, and cytochrome enzymes combine to produce the effects that are linked to herbs. These are some of the main mechanisms [17].

4.2Pharmacokinetic Interactions-

4.2.1 Pharmacokinetic absorption-

Chemotherapy patients frequently get intravenous oncolytic drugs. The kinetics of absorption are not changed by these drugs, which include tamoxifen, 5-FU, cyclophosphamide, and chlorambucil. A few drugs, such busulfan and imatinib, are taken orally to treat gastrointestinal tumors and leukemia; the presence of food may change how quickly the drug is absorbed. When giving medications orally, consideration should be given to the gastrointestinal pH, the amount of fluid present, the chemical and physical qualities of the medication, the type of food, and the gastric emptying time, as these can all result in therapeutic failure. Most anticancer treatments are prodrugs, which mean they need to be activated in the hepatic or gastrointestinal lumen to become their active form [18].

4.2.2 Enzymatic herb-drug interactions

The majority of xenobiotics and phytochemicals proceed through Phase I and Phase II metabolic pathways. Certain enzymes break down enzymatically during phase I reactions such oxidation and hydroxylation, changing the result into less polar metabolites in the process. The metabolites go through a phase II reaction that turns them into polar molecules that are easily excretable once the phase I reaction is complete. The majority of phase I metabolic processes are performed by an enzyme type known as cytochrome P450, often known as as peroxidases of cytochrome. They are primarily found in enterocytes and hepatocytes [19]. There are multiple families and subfamilies within CYP450. The primary activities of the cytochrome CYP3A family, of which the adult-expressing isoforms are CYP3A4 and CYP3A5, are intricate metabolic pathways connected to the metabolism of many allopathic Research has demonstrated that the combination of conventional and herbal drugs can both stimulate and inhibit CYP3A in vitro. It was well known that St. John's wort was a traditional herbal remedy utilized by cancer sufferers. St. John's wort decreased CYP3A4 in individuals receiving irinotecan medication, according to in vitro studies. Irinotecan's Cmax value increased as a result of CYP3A4 suppression, which eventually led to toxicity. The hepatocytes' mRNA expression was the reason behind these result. These outcomes were caused by the mRNA expression of the hepatocytes. On hepatocytes, St. John's wort contains quercitrin, hyperforin, and hypericin that interact with each other [21].

Conclusion

The majority of patients, according to study, are using complementary and alternative treatment, and some of them might also be taking herbal products. Physician supervision of the use of herbal products requires the implementation of effective guidelines. If there is an open discussion regarding whether or not herbal products are appropriate given the patient's current treatment phase and other options to provide as alternatives, patients may disclose using herbal products more readily and comply with their doctor's advise to discontinue using supplements when needed. An increase in herb-drug interactions is anticipated in oncology as complementary and alternative medicine becomes more widely used. In particular, it could be challenging to pinpoint decreased treatment efficiency caused by drug transporter and metabolizing enzyme activation. Treating doctors must therefore be aware of the possibility of drug interactions with complementary and alternative medicine. Sadly, not much is known or understood about how CAMs impact the induction of metabolizing enzymes and drug transporters. Using probe substrates, several

researchers have looked into how certain CYP enzymes are affected by herbs in healthy volunteers. Another drawback is that the majority of these research only examined the use of herbs for brief periods of time; nonetheless, continuous usage of herbs is particularly critical for induction. Based on the data currently gathered from these and other kinds of research, however, caution should be exercised when combining anticancer medications with various herbs, as CAMs all possess the ability to stimulate metabolizing enzymes and may result in undertreatment or increased toxicity in the case of prodrugs. Determining the roles of PXR, CAR, and VDR nuclear receptors could aid in developing new methods for examining the inductive potential of complementary and alternative medicine. The problem arises from the fact that complementary and alternative medicines (CAMs) are often made up of mixtures of several active components, and their exact composition is often unpredictable. The possibility that some CAMs are nuclear receptor antagonists is another crucial factor; this was demonstrated by the anticancer medication ET-743, which antagonizes PXR. This phenomena has not yet been investigated for CAM, nor have its effects been examined. The other receptors, CAR and VDR, should also receive more focus because they are as essential to the inductive process' mechanism. Ultimately, there is a dearth of data regarding the importance of the widely used CAM dose range for anticancer medication interactions in patients. Thus, it is crucial to evaluate the data from well-designed clinical studies that were collected using in vitro and in vivo methodologies. It can be difficult for doctors to have an honest discussion about herb-drug interactions with patients due to the wide range of possible interactions, their potential effects on clinical care, the paucity of research, and these variables. For interactions that result in modest problems or in a significant adverse event or treatment failure, a herb-drug interaction may be well tolerated. Therefore, in order to prevent cancer patients from receiving undertreated care or from experiencing unexpected toxicities, more study is necessary and should be encouraged to clarify the role of complementary and alternative medicine in undesired drug interactions.

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