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Review Article

Drug interaction of chemotherapy drugs and medicinal plants

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Abstract
The treatment of cancer is considered to be one of the most challenging problems in medicine. Amongst the most used treatments is the usage of herbal medicines, which helps both in prevention and cure of the disease. Although, the use of medicinal plants for treatment of cancer is harmless or even beneficial to patients but presents potential risk when combined with prescribed drugs. Drug interaction during cancer treatments therefore, is an issue that affects the Brazilian population. To analyze the drug interactions between chemotherapeutic agents and medicinal plants, a systematic literature review was performed with articles published in English and Portuguese between 2012 and 2019 from the databases such as PubMed and ScienceDirect. Search was carried out with the help of the Boolean Operator (AND) using following keywords: medicinal plants, drug interaction, chemotherapy, and herbal medicine. We found 149 articles in PubMed and 625 articles in ScienceDirect. The selection of articles for this study was done first by excluding repeated articles, then selecting articles by title, then by summary, and the last step was to read the full articles. Finally, twelve articles contributed to the research. A systematic research revealed that 5 medicinal plants, such as St. John's wort (*Hypericum perforatum*), Ginger (*Zingiber officinale*), Black cohosh (*Cimicifuga racemosa*), Celandine (*Chelidonium majus*) and Mango (*Mangifera indica*) containing metabolites such as polyphenols, alkaloids, flavonoids, saponins and others interacted with chemotherapeutic agents, such as irinotecan, tamoxifen, docetaxel and paclitaxel. In addition, many medicinal plants are used indiscriminately, without proper medical and pharmaceutical guidance in cancer treatment, to minimize side effects, such as nausea, headache and low immunity, that can cause harm to the patient.
Keywords: Medicinal plants, Chemotherapy, Interaction, Cancer

Introduction

It is important to note that one of the most diverse diseases that affects the population in the world is cancer as reported by the Union for International Cancer Control (UICC). By 2020 there will be a 50% increase in the number of new cancer cases and twice the number of deaths. In some countries like Brazil, this situation would be even more challenging, because the survival rate of patients with cancer is around 2 to 4 years, while in developed countries this rate ranges between 12 to 16 years.[1] In this context, one of the treatment strategies used in the patients with cancer is chemotherapy, using medicines with the function to combat and control modified cells that form tumors. Therefore, various side effects arise during the cancer treatment, such as fatigue, hair loss, nausea and anemia. The search for ways to combat these side effects are sought by the patients themselves, without consultation with a healthcare professional, and they use medicinal plants to help with the treatment. Even with the encouragement of the pharmaceutical industry to the use of allopathic medicines by the patients, a large part of the population uses alternative therapeutic care such as medicinal herbs to alleviate or treat the disease. This might be on account of high cost of allopathic medicines or because users are looking for alternatives that have fewer side effects for treating diseases.[2,3]

However, the development of possible interactions between herbal preparations and other concomitantly administered chemotherapeutic agents can be very problematic and may lead to undesirable several side effects. Pharmacokinetic interactions between medicinally active plants and chemotherapeutic agents may cause changes in

release, absorption, distribution, metabolism, excretion or toxicity during anti-neoplastic treatment. Plant extracts also have the possibility of causing pharmacodynamic interactions with receptors and enzymes, leading to undesired pharmacological action and even blockage of cell mechanisms.[4,5]

An analysis based on the selected species of medicinal *plants (H. perforatum, Z. officinale, C. racemosa, C. majus* and *M. indica)* shows the importance of understanding the ability of medicinal plants to modulate metabolizing enzymes and that it is essential for a safe and responsible treatment of cancer patients. Cytochrome P450 protein complex (CYP) enzymes are protagonists in metabolism of Phase I and are also involved in the oxidation and elimination of xenobiotics (substances foreign to the body such as drugs and toxins). The drug metabolism involves about 15 different CYP isoforms, in which CYP 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 are the most prevalent.[5-7] After that, xenobiotics become acid conjugated with glucuronic acid, sulfate or amino acids, which in turn, are eliminated by the kidney and passed through urine.[6,7]

Materials and Methods

The literature search was performed on December 17, 2019, in the PubMed databases, for scientific articles published from 2012 to 2019 which reported plants interacting with chemotherapy metabolism. We used the following combinations of descriptors and connectors: "chemotherapy" AND "medicinal plants" and "herbal medicine" AND "drug interaction". Then, the selection by titles was made using only those that referred to some contribution to the objective of this work. In the third stage of article selection, the abstracts of the articles selected in the previous stage were read, among which those who did not use medicinal plants or did not relate to the pharmacokinetic and pharmacodynamic mechanisms of plant-drug interaction were excluded. The results of the articles at this stage were read in full and, therefore, those articles were selected which contributed to the data that allowed explaining interaction of plant-drug with cancer patients who used chemotherapy. This article aims to show that some medicinal plants that are often presumed to be safe and not causing any undesirable effects may actually be harmful, and if not monitored properly, can complicate the health of patients undergoing cancer treatment.

Results and Discussion

Most of the data collected for this study were obtained from ScienceDirect followed by PubMed databases. However, not all the articles were made available on these websites displaying the error flag on the page. The quantitative data of results displayed and used after each article selection step are presented in Table 1.

Considering the amount of data available, the database that presented the highest absolute number of articles was ScienceDirect (326), although PubMed showed the highest utilization (A%) in all selection stages. This means that even though PubMed provided a smaller number of articles initially, its results were more relevant. The search provided 12 full reading articles that contributed to this study.

The experimental data that contributed the most to determine the validity of the hypothesis of this study is summarized in Table 2.

It is estimated that approximately 60% of cancer patients use alternative methods for treating their diseases, including herbal medicine.[8] In this context, the use of medicinal plants in patients who use chemotherapy seems to be a common practice. Moreover, medicinal plants contain phytochemicals that can cause interactions with conventional drugs. In the study by Gorman et al[9] 1000

Table 1. Data for quantitative monitoring of articles at each stage of selection

Results Reported in the Databases			PubMed	ScienceDirect	Total	Selected Articles (%)
			149	**625**	**774**	
Results displayed		N°	145	326	471	-
		%T	30.7	69.2	-	-
After Copies deleted		N°	139	280	419	88.95
		%T	33.2	66.8	100	-
		A%	95.8	85.9	88.95	-
Selection Step	1. Titles Read	N°	55.0	20.0	75	16.1
		%T	73.3	26.7	-	-
		A%	37.9	6.13	15.92	-
	2. Abstracts Read	N°	26.0	8.0	34	49.3
		%T	76.5	23.5	-	-
		A%	17.9	2.4	7.21	-
	3. Full Articles Read				**12**	**2.54**

N° - number of articles obtained or selected in each stage of the work; %T - percentage of articles in the database in relation to the total available or selected in each step; A% - Percentage of articles used, after each selection step, in relation to the number of articles available in the database.

mg (three times a day) of St. John's wort (*H. perforatum*) aerial parts extract containing hyperforin was reported to inhibit the enzymatic coding of CYP2D6, 3A4 and 2C9, 2C19 demonstrating the importance of rational use of medicinal plants that are commonly consumed by patients along with chemotherapeutic drugs like tamoxifen or irinotecan, which are metabolized by CYP450 enzymes.[9] Research reports suggest that the extracts obtained from *H. perforatum* containing hyperforin and flavonoids proved to be potential inhibitor of CYP3A4, and when co-administered with medicinal products, metabolized this enzyme leading to decrease in clearance and increase in plasma concentrations (AUC).

Since St. John's wort also induces the expression of CYP3A4 and the trans-membrane transporter PGP protein (P glycoprotein) in the liver and intestines it shows pharmacokinetic changes in medications. Almjade et al[10] have reported a reduction in bioavailability, half-life and maximum concentration of a single dose of Imatinib when combined with *H. perforatum* leaf extract. Ten milligram of extract of the leaves of *H. perforatum* which was mixed with 5 mL of 70% methanol under constant agitation was able to inhibit CYP3A4, however, the enzymes CYP2D6, CYP1A2, CYP2C9 and CYP2C19 may also be involved. Irinotecan is known as a prodrug metabolised by CYP3A4 and CYP3A4. Induction by *H. perforatum* extracts had reduced impacts on plasma concentration of irinotecan metabolites. Goey et al[11] have also reported the interaction of *H. perforatum* with chemotherapeutics such as docetaxel and paclitaxel suggesting that they require the activities of enzymes CYP2C8 and CYP3A4 in the liver, therefore, the leaves of *H. perforatum* have the ability to alter its pharmacokinetics.

Gorman et al[9] have reported that ginger (*Z. officinale)* having phenylpropanoids, sesquiterpenes and gingerols acts on the pharmacokinetics of tamoxifen-mediated chemotherapeutic agents and the activation of carboxyesteresterase, at the dose of 1000 mg root extract consumed 3 times a day. Also, the use of Black cohosh (*C. racemosa)* inhibits CYP2D6 in healthy volunteers treated with 1090 mg twice daily, each capsule standardized for triterpene glycosides. The bioactive components of Black cohosh leaves were identified as triterpene glycosides, 27-deoxyactein cimiracemoside A and isoflavone, formononetin and other polyphenol compounds. The *C. racemosa* was considered the most potent inhibitor of tamoxifen and irinotecan bioactivation, as it inhibits pharmacodynamics by binding to estrogen receptors. The action of polyphenols has also been described by Ashour et al.[12] They have characterized polar and charged

Table 2. Summary of the articles analyzed and results obtained about the plant-chemotherapy interaction

Study Reference	Plants	Part of the Plant	Therapeutic Indication	Interacting Plant Metabolites	Reaction Type	Inhibited Elements	Interaction with Chemotherapeutics
Rodeiro et al, 2012	*Mangifera indica*	Stalk	Antioxidant, Analgesic and Anti- inflammatory	Alkaloids, flavonoids and saponins	Pharmacokinetics	CYP1A2, 2A6, 2C9, 2D6, 3A4	Chemotherapeutics that are metabolized by the enzymes mentioned above
Gorman et al, 2013	*Hypericum perforatum*	Sheeds	Laxative, Diuretic, Soothing and Pain killer	Hyperforin	Pharmacokinetics	CYP2D6, 3A4, 2C9, 2C19	Tamoxifen and irinotecan
	Zingiber officinale	Root	Pressure regulation, nausea and anti-inflammatory	Phenylpropanoids, sesquiterpenes and gingerols			
	Cimicifuga racemosa	Sheeds	Loss of appetite, Tiredness and Nausea	Triterpenes, acetone, deoxyacin, cyimiracemoside A and isoflavone, formononetin	Pharmacokinetics and Pharmacodynamics	CYP2D6 and estrogen receptors	
Goey et al, 2014	*Hypericum perforatum*	Sheeds	-	-	Pharmacokinetics	CYP2C8, CYP3A4	Docetaxel and paclitaxel
Liu et al, 2018	*Chelidonium majus*	Sheeds	Analgesic	Quinidine	Pharmacokinetics	CYP2D6	Doxorubicin and tamoxifen
Showande et al, 2018	*Mangifera indica*	Stalk	Analgesic, Antioxidant and Anti-inflammatory	Alkaloids, flavonoids and saponins	Pharmacokinetics	CYP2C8, CYP2B6, CYP2D6, CYP1A2, CYP2C9	Chemotherapeutics that are metabolized by the enzymes mentioned above
Almjade et al, 2019	*Hypericum perforatum*	Sheeds	Analgesic and Soothing	-	Pharmacokinetics	CYP3A4	Irinotecan

polyphenols as molecules that interact with proteins forming ionic bonds, as well as hydrogen bonds with various amino acids at the active site. This means that it can lead to enzyme inhibition and loss of function, being able to interact with Cytochrome P450. Celandine *(C. majus)* is believed to have originated from Europe and Asia, known as wart weed, swallow weed. Its leaf infusion is mainly indicated for its analgesic effect, widely used by cancer patients. In a research by Liu et al,[13] the inhibitory effects of celandine leaf extract on human cytochrome P450 enzymes that act on drug metabolism as well as chemotherapeutic agents were evaluated. Quinidine, alkaloid, may be a competitive inhibitor of CYP2D6 responsible for the metabolism of some chemotherapeutic drugs such as doxorubicin and tamoxifen, attenuated the enzyme inactivation, with potential for drug induction.

In the experimental study conducted by Showande et al,[14] 300 g of mango (*M. indica*) stem barks was mixed in 1.5 L of distilled water for 24 hours, then lyophilized extracts were stored at 20°C until the time of usage for *in vitro* analysis. Stem metabolites are alkaloids, flavonoids, saponins which indicated moderate inhibition of CYP2C8, CYP2B6, CYP2D6, CYP1A2 and CYP2C9.[13] An another study conducted by Showande et al,[14] confirmed the research by Rodeiro et al[15] in which it was reported that the aqueous extract of *M. indica L.* stem bark decreases the activity of some cytochrome P- 450 (P450) in rat hepatocytes and human liver microsomes. There was a concentration-dependent decrease in activity of P450 measured CYP1A2 enzymes Similar effects were also observed in enzymes 2A6, 2C9, 2D6 and 3A4. For all the activities, a reduction of at least 50% at the highest concentration (250 µg/mL) was recorded.

Conclusions

This study has allowed us to realize the importance of medical monitoring to avoid the use of herbal medicines that can interact with chemotherapy and hamper the process of cancer treatment patients and compromise their health. As already mentioned in Veiga & Pinto[16] and Simões et al,[17] medicinal plants can be used for treatment and prevention of diseases, since it is one of the practices of medicine and pharmacy based on a knowledge that has existed for many years. It is important to note that all medicinal plants are not harmlessness. Differently from the expression "natural is good", as most people think, a medicinal plant may act as a xenobiotic, a foreign element to the body that when inserted into the human system undergoes changes and alterations in metabolism and can generate harmful products.[6,17] Therefore it is necessary to pay attention and follow up with the health profession, such as doctor, pharmacist and a homeopath, making sure that the plant does not interfere with the healing process of the patients. As revealed in this systematic study, there are interactions between secondary metabolites of the plants St. John's wort (*H. perforatum*), Ginger (*Z. officinale*), Black cohosh (*C. racemosa*), Celandine (*C. majus*) and Mango (*M. indica*) that are consumed as food or for medicinal purposes and chemotherapeutic agents, moreover, the interaction might be through pharmacokinetic and pharmacodynamic mechanisms. In this context, interaction between all the selected plants and chemotherapeutics was verified, and the interaction occurred mainly by inhibiting or delaying the action of the cytochrome P450 enzyme complex.

Competing Interests

None

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