

# Oncological Patients Under Therapy and Potential Risks Associated to Interactions with Natural Products for Constipation Relieve

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## Abstract

**Background:** Some oncological patients tend to have constipation. To relief this symptom, they are induced to take natural products which could be responsible for herb-drug interactions, and give unexpected therapeutic effects. In this paper we will discuss, as examples, clinical events resulting from the concomitant use of these products and chemotherapy.

**Methods:** The study was performed based on the critical analysis of real clinical cases occurred with the patients followed at the Observatory of Herb-Drug Interactions, head office in Faculty of Pharmacy University of Coimbra (OIPM/FFUC; www.oipm.uc.pt), in collaboration with the Oncology Hospital (Portuguese Institute of Oncology).

**Results:** From the data collected the risk of inefficacy of the treatments could be from the intake of mucilaginous products and anthraquinone derivatives. The first can reduce the absorption of the oral chemotherapy, as Tamoxifen, used concomitantly. In this group the predominance goes to seeds as Chia, Flaxseed, Hollyhock and Plantains and other mucilaginous products as Algae and Mallow. The second group corresponds to herbs with anthraquinone derivatives that were many times the first choice due to its intense laxative activity. These compounds are present in plants as Aloe, Buckthorn and Sene. They can decrease absorption of drugs, especially the ones that have low oral absorption and, consequently, they can cause an inefficacy of the treatment. Pharmacodynamic interactions can also occur. For example, extracts of Aloe are capable to promote angiogenesis and inhibit irreversibly CYP3A4 increasing plasma concentration of drugs or even decreasing active metabolites from pro-drugs.

**Conclusion:** Oncological patients are easy targets for marketing such products and may be victims of dangerous interactions that, at the limit, can result in death. Furthermore, it is important that doctors are also aware of these questions to help in the identification of problems and avoid failure of treatments by inefficacy or increase of toxicity effects. The discussion carried out in this paper will serve as a preliminary alert about the issue that can be used to perform further studies.

## Introduction

Pharmacoepidemiologic studies, carried out in Europe and Americas found varying rates of potential drug-drug interactions (DDIs), ranging from 5% to 80% [1–6] and the factors that have shown are consistent in the association with this presence, nevertheless a lack in information in herb-drug interactions based on clinical reports remain scarce. It is estimated that prevalence of consumption of herbal medicines during chemotherapy is greater than 35% in United States of America and it can be greater than 50% in developing countries [7].

According to a study in Middle Eastern, between 20 and 70% of herbal medicine users do not inform their doctors [7]. Furthermore, they are often not aware of natural products used by their patients [11]. These are the most affected in this poor communication. As an example, most of them tend to have constipation problems due to medications and sedentary life which is many times required during the treatments [8]. To relief this situation they are induced to take natural products that are popular among the general population due to the generalized idea that they are innocuous [9–11]. Nevertheless they can cause important herb-drug interactions which sometimes may result in lack of therapeutic effect of the chemotherapy. Depending of the products involved (herbs and drugs) they also can induce an increase of side effects [9,12]. The change of this scenario is imperative and it is necessary to inform patients and health care professionals about the risk of concomitant intake of drugs and herbal products.

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In this paper we will give examples that can happen with the use of natural products to relief constipation based on real clinical cases that occurred with the patients followed at the Observatory of Herb-Drug Interactions/ Faculty of Pharmacy University of Coimbra (OIPM/FFUC; www.oipm.uc.pt), in collaboration with the Oncology Hospital (Portuguese Institute of Oncology). The treatment of oncological patients is often associated to complex events and the discussion carried out in this paper will serve as a preliminary alert about the one of the issues and can be used to perform further studies.

## Materials & Method

The study was observational and the results given are an evidence based medicine approach. The data was extracted from all the clinical cases involving oncological patients with constipation in follow up of the OIPM/FFUC. The reports carried out for each patient were based

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on symptoms, constitution of the natural products and concomitant use of drugs. Information from the literature was carried out on different databases such as DrugBank<sup>®</sup>, Medscape<sup>®</sup>, PubMed<sup>®</sup> and Medline<sup>®</sup> were consulted between March 2011 and October 2013 using the search terms “antracenic”, “antraquinone”, “mucilage”, “herbs”, “CYP”, “herb-drug” and “interactions”, as so, the specific terms of each particular clinical case, in order to identify citations, abstracts and articles. Some more specific information about each plant was also collected from databases such as Natural Medicines Comprehensive Database, National Centre for Complementary and Alternative Medicine and Medscape Reference.

Ethical and Clinical permission regarding the study was approved in May 2009 included in the project “IciPlant – Interactions between cytostatic drugs and Plants” developed at the Coimbra Oncologic Hospital and coordinated by the Observatory of herb-drug interactions (2009-2020). The data on here provided belong to preliminary approach to the issue and for that reason no statistical data to provide.

## Results

In present work, we will focus on oncological patients that are one of the several risk groups of herb-drug interaction. In Portugal, in the last decade, the prevalence of patients with cancer increased. In 2015, there were about 50,000 patients [13]. The medications to treat cancer include different drugs and the most of them with narrow therapeutic index and used at dosages near to toxic level [14]. Any change to the plasma concentrations will cause a unexpected event and one of the common situation is the intake of natural products. Oncological patients belief that these products (a) can kill cancer cells, (b) can treat symptoms related with cancer disease or (c) reduce the side effects of antineoplastic drugs [10]. Users of this kind of products often believe that these products have not adverse effects. From our experience, we verified that among the clinical cases involving oncological patients at the Observatory of Interactions Herbal-Drugs (OIPM/FFUC - Portugal), many of them complain about constipation and ask for natural products to relief these symptoms. Constipation can be classified in primary, if there is not a pathological cause, or secondary to other diseases or drugs [8]. Causes of primary constipations can be modification of daily routine, dehydration or pregnancy and secondary constipation can be caused by diseases or drugs [8]. In Table 1, we resume some pharmacotherapeutic groups that can cause constipation as side effect. mobilisation and traction of the cardia (Table 1).

Drugs	Constipation mechanism
Opioid analgesics	
	Inhibition of peristalsis which prolong intestinal transit, causing increased absorption of water and electrolytes and lower response of defecation.
Antidepressive	Especially tricyclic antidepressants, due to anticholinergic effects.
Antimicrobial	Peripheral neuropathies.
Antiparkinson	Anticholinergic effects.
Antiepileptic	Anticholinergic and dopaminergic effects.
Antineoplastic	Peripheral neuropathies. (In few times can change intestinal innervation).
Antipsychotic	Anticholinergic effects.
Antihypertensive	Reducing smooth muscle contractility.

Table 1: Principal groups of drugs which cause constipation [8].

From the data collected in our clinical reports, the most popular products used by oncological patients to relief constipation were: seed, from Chia (*Salvia hispanica*), Flaxseed (*Linunusitissimum*), Hollyhock (*Althaea officinalis*) and plantains (*Plantago sp.*) and other mucilaginous plants as Algae (*Gelidium sp.*) and Mallow (*Malvasylvestris*). All of them can reduce the absorption of the oral chemotherapy, as Tamoxifen, if ingested together due to the mucilage content.

Antraquinone derivatives from plants as Aloe vera (concentrated juice of leaves), *Rhamnusfrangula* (bark), *Rhamnuspurshianus* (bark) and Sene (*Cassia acutifolia*, leaves and fruits) were also used by the patients. These herbs can stimulate the intestine increasing the intestinal transits which decrease the absorption of drugs, especially the ones that are difficult to absorb.

From clinical reports, several potentially negative herb-drug interactions were identified. Most of herb-drug interactions are pharmacokinetics interactions. In some cases, pharmacodynamic interactions can also occur. For example extracts of Aloe are capable to promote angiogenesis[15], and inhibit irreversibly CYP3A4[16] increasing plasma concentration of drugs that will increase side effects, unless they are pro-drugs and in this situation the drug, active metabolite, will be not available for treatment once is not metabolized in the effective dose.

In Table 2, we resume the principal herbs used by oncological patients to relieve constipation and potential negative herb-drug interactions. Note that generally, natural products are complex mixtures of phytochemicals what increase the difficulty to analyze the effect.

\* Chemotherapy drugs have narrow therapeutic window. Small changes in the pharmacokinetic parameters can reduce efficacy or increase side effects[29,30].

\*\* Anthraquinone derivatives cause irritation of intestinal mucosa. It can cause abdominal pain. The laxative action results from inactivation of the Na<sup>+</sup>/K<sup>+</sup> pump and inhibition of chloride channels, decreasing the reabsorption of water. These derivatives also induce release of mediators that stimulate the contraction of smooth muscles of the intestine (eg, histamine)[31].

## Discussion

For a better understanding of these events in the text below, the discussion will be divided in 3 points. First mechanisms of potential interactions of main natural products for relief constipation used by oncological patients; second the risks associated with the use of anthraquinone derivatives; to finish an example of a case report will be given to elucidate the evaluation of Green tea as the cause obstipation, what is a different approach to this issue but usual in this patients too.

The pharmacokinetic modulation seems to be the most common mechanism of herb-drug interaction[10]. In our study, the mechanisms of interaction more common are: (a) reduction of absorption due to retention in dietary fibers or a faster intestinal transit (laxative effect, of anthraquinone derivatives for example); (b) modulating the activity of CYP450, in the liver (mainly due to phenolic compounds). However, pharmacodynamics interactions can occur too (eg. promotion of angiogenesis).

HerbalDrugs	Compounds	Mechanismofinteraction	Comments
Chia seeds ( <i>Salvia hispanica</i> , seeds)	Dietary fiber	Reduction of absorption of organic molecules[17]	* Tamoxifen has very low oral absorption and biotransformation in CYP 3A4 and 2C9. The inhibition of these enzymes decreases the production of the bioactive metabolite what could result in a therapeutic failure. Other chemotherapy drugs that are metabolized or activated in these isoforms of Cytochrome P450 could also be affected[18].
	Phenolic Compounds	Inhibition of CYP 3A4 and CYP 2C9[17,19]	
Flaxseed ( <i>Linunusitatissimum</i> , seeds)	Mucilage and pulp	Reduction of absorption of organic molecules[20,21]	* In breast cancer, it can promote hormone-dependent tumor growth (data not conclusive, but important alert) due to its estrogen-like effect. It also interferes with metabolizing of testosterone[22].
	Phytoestrogens	Inhibition of CYP 3A4[23] Estrogen-like activity[24]	
Plantains ( <i>Plantago</i> sp., seeds)	Mucilage	Reduction of absorption of organic molecules[20]	*
Chlorella ( <i>Chlorella ellipsoides</i> )	Mucilage	Reduction of absorption of organic molecules[20,21]	* These products could be contaminated with other algae that produce toxins. (we had a unique event, that occurred with an oncological patient that suffered toxic hepatitis associated to chemotherapy and a microcystin that was in a contaminateda Chlorella supplement - case report submitted to publication)[25].
Rhubarb ( <i>Rheum officinale</i> , root)	Anthraquinone derivatives and tannins	Reduction of absorption and inhibition of CYP 1A1[26]	* **
<i>Rhamnusfrangula</i> and <i>Rhamnuspurshiana</i> (bark)	Anthraquinone derivatives	Reduction of absorption[23,27]	* **
<i>Aloe barbadensis</i> (concentrated juice of leaves)	Anthraquinone derivatives	Inhibition CYP 3A4[16] and reduction of absorption[27]	* ** Inhibition of CYP3A4 is irreversible[16].
	$\beta$ -sitosterol	Promotion of angiogenesis[15]	Inhibition of angiogenesis it is a strategy of some chemotherapy schemes[28]. The intake of product that do the inverse effect could be problematic.
Sene ( <i>Cassia acutifolia</i> , leaves and fruits)	Anthraquinonederivatives	Reduction of absorption[21]	* **
Konjac ( <i>Amorphophalluskonjac</i> )	Glucomanan, mucilage and pulp	Reduction of absorption[20,21]	*
Guar gumming ( <i>Cyamopsistetragonolobus</i> )	Mucilage and pulp	Reduction of absorption[20]	*

Table 2: Herb-Drug interactions examples

The herb-drug interactions identified can be potentially negative because they may modify absorption, metabolism, distribution and/ or elimination of anticancer drugs. However, we must be careful when drawing conclusions. Sometimes, the data found in literature are from *in vitro* studies and several factors can complicate the extrapolation of these data, like poor solubility and gastric degradation of phytochemicals compounds or lack of standardization of natural products [11].

Goey et al., refer that doctors should always ask their patients about use of natural products before starting chemotherapy. If they use these products, the physician should consult preferentially clinical studies to verify if the concomitant use with chemotherapy is safe [11].

From the products used to constipation relief, a special attention should be given to the use of anthraquinone derivatives. These compounds should not be administered in case of known hypersensitivity to the active substance or in case of intestinal disorders like obstructions and stenosis, atony, inflammatory diseases. It is necessary to have especially careful in case of: (a) pregnancy (it can induce abortion by stimulation of receptors of oxytocin); (b) lactation (it is excreted in breast milk and it can cause diarrhea in children); (c) concomitant use with cardiotoxic drug (hydroxyanthracenes can cause loss of potassium and it potentiate action of cardiotoxic drug); [4] taking oral contraceptives (risk of lower intestinal absorption) [31,32].

In OIPM/FFUC, we note that a lot of patients (not only oncological patients) consumed natural products which contain anthraquinone derivatives. Some of these products are marketed as food supplements. In 2013, European Food Safety Authority (EFSA) published a scientific opinion associated with a health claim related to food supplement with hydroxyanthracene derivatives to improve bowel function. The EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) give the note that “the established effect of hydroxyanthracene derivatives from the root and rhizome of *Rheum palmatum* L., *Rheum officinale* Baillon and their hybrids, from the leaves or fruits of *Cassia senna* L., *Cassia angustifolia* Vahl, from the bark of *Rhamnus frangula* L., from the bark of *Rhamnus purshianus* D.C. and from *Aloe barbadensis* Miller and various *Aloe* spp, mainly *Aloe ferox* Miller and its hybrids is well established on the short-term alleviation of occasional constipation”. In relation to the restrictions of use, they highlight that contact laxatives should not be used for periods longer than one or two weeks. The use of laxatives for more than this period requires medical supervision [33]. Use of stimulant laxatives for long time should be avoided by contraindications above pointed out. These products should only be used if an effect on bowel function cannot be achieved by a change of diet or the administration of bulk forming agents [33].

To exemplify a different situation from the previous discussion, we report a clinical case where green tea was the cause of obstipation in an oncological patient. A Caucasian woman with breast cancer, medicated with Tamoxifen began to ingest green tea aiming to lose weight. After that, she began to complain of constipation. We analyzed the case and concluded that green tea was the cause of this constipation. Constipation could be a side effect of Tamoxifen [18], but there was not constipation before she began taking green tea, because she used to consume Chia seeds to regularize the intestinal transit. In high amounts (more than 2 liters per day), green tea can cause dehydration due to theophylline that explains the onset of constipation [34]. She stopped taking green tea and symptoms disappeared. However, she was advised that Chia seeds could interfere in the metabolization of the drug. They can inhibit CYP 3A4 and CYP 2C9 [17,19] and they also can reduce the oral absorption of drugs, as explained above. The physician responsible for this patient was also informed of the situation.

## Conclusion

Oncological patients often use natural products including laxative ones and may be victims of dangerous interactions that, at the limit, can result in death. Furthermore, it is important advise them to do secure medications to treat their symptoms and to increase their health-related quality of life.

In Portugal, patients do not often report to their doctors that they use this kind of products. As patients do not share this information with their doctor, it becomes more difficult to detect and prevent these interactions. A proactive intervention of health professionals recommending precaution to its patients probably could prevent some complicated situations.

Nevertheless, patients should be conscious also and they must report his medication to pharmacist, or other health care professional, before the intake of herbal drugs, even when they take them as self-medication. With these precautions, we hope to avoid situations more serious and harmful for them and improve their quality of life.

Health care professionals should be conscious about the risk of intake herbal drugs concomitantly with chemotherapy drugs and other drugs, particularly in cases of polypharmacy situations or with small therapeutic windows. Doctors, pharmacists, nurses and other health care professionals should know the risks of herb-drug interactions and what they can do to avoid serious damages to patients. The follow up of these situations and the report of them is a very important tool to get more information for further guidelines.

## Competing Interests

The authors declare that they have no competing interests.

## Author Contributions

Nuno R. Jesus, MSc- contribution to conception and design, acquisition of data, analysis and interpretation of data, involvement in drafting the manuscript, revising it critically for important intellectual content.

Cheila Batista, MSc- acquisition and analysis of data

Cátia M. Silva, MSc - acquisition and analysis of data

Tiago P. Silva, MSc - acquisition and analysis of data

Maria Luísa Costa, MSc - contribution to conception and design, acquisition of data, analysis and interpretation of data.

Maria Helena Gervásio (Doctor, Director of the Oncology Service at the Oncologic Hospital)- acquisition and analysis of data at the Oncologic Hospital

Maria da Graça Campos, PhD (Pharmacist, Director of the OIPM/FFUC)- contribution to conception and design, analysis and interpretation of data, involvement in drafting the manuscript, revising it critically for important intellectual content.

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