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Article

Phytotherapy Use to Treat Chemotherapy-Related Side Effects in Lung Cancer Patients

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Abstract: Phytotherapy has been used since ancient times for the treatment of many diseases, one of the fields of greatest use is oncology. Thus, patients use herbal medicines to counteract the side effects of chemotherapy, however these remedies, although natural, can lead to interactions if taken simultaneously with other medicines. The aim of the study was to identify interactions that may arise in the intake of oral chemotherapy in conjunction with phytotherapeutic substances This was a retrospective and descriptive study conducted among lung cancer patients actively undergoing chemotherapy. Data collection was conducted through the distribution to patients of a self-compiled and closed-ended questionnaires during chemotherapy treatment. Data relating to 35 patients were collected and interviews were collected for a total of 66 accesses to the facility. It was found that 69% take at least one phytotherapeutic substance. Among the most used substances we found green tea, 26% of accesses, and ginger, 30% of accesses. Some statistically significant comparisons were between chamomile and mucositis intake, turmeric and epigastric pain and sex differences considering diarrhea and headache. Obtained data confirmed that phytotherapics can increase the toxicities caused by chemotherapy.

Keywords: complementary medicine; supplement; food; sex differences; toxicity

1. Introduction

The most up-to-date global data for 2020 estimate that lung cancer (LC) is the second most diagnosed cancer with 2,206,771 (11.4%) new cases, and the most common cause of cancer death with 1,796,144 (18%) deaths globally [1]. This mortality has two main causes, delay in initial diagnosis, with most new diagnoses showing advanced disease, and poor overall survival. There are 2 main forms of LC: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) [2]. There are sex differences in the incidence and mortality of LC [1]. For men, it is the most incident and fatal cancer: 1.44 million of new cases (14.3%) and 1.19 million of deaths (21.5%) globally. For women, however, LC is the third for incidence with 770,828 (8.4%) new cases and the second deadliest with 607,465 (13.7%) of deaths globally. The incidence of LC has increased dramatically in women over the last 50 years. Diagnosis for LC is more frequent at a younger age in women than in men [3]. Several studies have found a higher risk of LC for women who smoke than for smoking men. In addition, significant mutations that may be caused by tobacco carcinogens have been found more frequently in women than in men. Studies have shown that the tumor protein p53 (TP53) gene is mutated into more than two thirds of LCs, and that mutations are more frequent in women [3].

For the treatment of LC, the main therapy used is platinum-based chemotherapy and its derivatives. However, this therapy shows main limitation as adverse reactions and numerous side effects. Chemotherapeutics are also conditioned by the various interactions with the simultaneous

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intake of phytotherapics and, above all, foods [4,5]. Until now, the main identified interactions can be classified into two broad categories: enzymatic interactions, due to the ability of many herbs to bind enzymes belonging to the cytochrome p450 (CYP) family, capable of metabolizing numerous drugs and interactions with glycoprotein P, encoded by the human gene multi drug resistance 1 (mdr1), which has a key role in the resistance phenomena associated with chemotherapy: it acts as an efflux pump, causing the expulsion of anticancer drugs from cancer cells and it is also responsible for the systemic distribution of drugs, toxins and carcinogens of various organs [6,7].

Since few studies in literature analyses the interactions between phytotherapics and chemotherapeutics, we aimed to describe the phytotherapeutic substances and foods taken by a group of patients with LC, undergoing oral chemotherapy. In addition, in this population, we collected information about the most frequent side effects, analyzing data desegregated by sex, to assess whether there may be variability of adverse effects between men and women.

2. Materials and Methods

The prospective observational study was carried out in the period between January and August 2020 in the hospital "Molinette" of the University Hospital City of Health and of Science of Turin, in the day hospital of the Oncology Department within the Centro Oncologico Ematologico Subalpino. In order to achieve the aim of the study, a database has been built in which the data were collected through the distribution of a questionnaire, designed whit the consultation of numerous experts (nurses, pharmacologists and oncologists). In the study were included patients with LC taking chemotherapy orally and patients monitored at every access.

Through a review of the literature, phytotherapeutic and nutraceutical products were selected. For the purpose of the study, the variables investigated were divided into macro-areas. The data included were: sex, age, weight, height and the index of Performance status, defined by the Eastern Cooperative Oncology Group (ECOG, [8]) that evaluates the general condition of patients. Then the data about the drugs taken by the patient in conjunction with chemotherapy were collected. In the last section of the questionnaire, the phytotherapeutic substances, the foods taken, and the toxicity recorded were assessed. The data has been entered in a database, analyzed through questionnaires and medical and nursing records via the TrakCare system (InterSystems Corporation, Cambridge, MA).

The selected drugs were: Dexamethasone, Hydrocortisone, Aprepitant, Metoclopramide, Ondansetron, Paracetamol, Codeine, Fentanyl, Tramadol, Amlodipine, Diltiazem, Irbesartan, Lercanidipine, Losartan, Nebivolol, Nifedipine, Nitrendipine, Propranolol, Verapamil, Atorvastatin, Cerivastatin, Fluvastatin, Lovastatin and Simvastatin. The selected phytotherapics were: hypericum, propolis, ginger, turmeric, eucalyptus, garlic, sage, Boswellia, valerian, licorice, astragalus, aloe, tobacco, horse chestnut, milk thistle, oats, ginkgo, mistletoe, green tea, chamomile, echinacea, soy, ginseng, cannabis, mint, goji berries, charcoal, cardamom, linseed oil, Passiflora, uncaria and withania. The selected foods were: broccoli, grapefruit, garlic, pomegranate, oats, pineapple, vinegar, milk, lemon, fennel, papaya, chili pepper and cabbage. Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 for toxicity were used: nausea, vomit, neurotoxicity, alopecia, asthenia, diarrhea, constipation, “hand-foot” syndrome, epigastralgy, dysgeusia, thrombocytopenia, epistasis, mucositis and neutropenia [9]. For each phytotherapeutic substance and nutraceutical were considered the frequency of intake (daily, 2/3 times a week, 1 time a week, monthly) and the form (pearls, herbal teas, syrup, capsules, granules and more); moreover, it was investigated how the patient have known the herbal products taken (acquaintance; medical; websites; herbalist; pharmacist; other).

Continuous variables were described using mean and standard deviations (SD) or median and interquartile range (IQR) according to their distribution. Categorical variables were described using frequencies and percentages. Differences between males and females were tested performing the Mann-Whitney U test or the Fisher exact test, when appropriate. Multivariate logistic regression models, adjusted by age, were computed to evaluate the association between sex and risk of toxicity during chemotherapy treatment. The Huber-White estimator was used to adjust for the correlation

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between the multiple observations on the same patient. Odds Ratios (OR) and 95% confidence intervals (95% CI) were reported. Firth's correction was applied to reduce the bias of the estimates due to small number of events. Statistical analyses were performed using IBM SPSS Statistics 22.0 per Windows (Chicago, Illinois, USA). The level of significance was set at 0.05.

3. Results

Data were collected from 35 patients (15 were women and 20 men) for a total of 66 accesses (36 were women and 30 men). The average age of the sample is 62.44 years ± SD 13.99. The distribution by sex is 57.14% of men and 42.86% of women, however, more women replied to the total questionnaires. Patients demographical, clinical and pharmacological characteristics were resumed in Table 1.

Table 1. Demographic, clinical and pharmacological characteristics of patients.

Patients (N)	**35**
Age (median (IQR))	67 (53.25-72.75)
Males (N (%))	20 (57.14)
Body Mass Index (median (IQR))	24.55 (22.77-26.59)
Accesses (N)	66
Males (N (%))	30 (45.45)
Drugs (N (%))	
Hydrocortisone	4 (6)
Dexamethasone	9 (14)
Metoclopramide	4 (6)
Ondansetron	1 (2)
Paracetamol	23 (35)
Codeine	5 (8)
Fentanyl	2 (3)
Tramadol	2 (3)
Amlodipine	3 (5)
Nebivolol	1 (2)
Atorvastatin	4 (6)
Simvastatin	1 (2)
Other	41 (62)
Phytotherapics (N (%))	
Propolis	8 (12)
Ginger	20 (30)
Turmeric	8 (12)
Eucalyptus	4 (6)
Garlic	17 (26)
Sage	9 (14)
Valerian	3 (5)
Licorice	7 (11)
Astragalus	1 (2)
Aloe	11 (17)
Oats	4 (6)
Green tea	17 (26)
Chamomile	19 (29)
Echinacea	2 (3)
Soy	12 (18)
Cannabis	1 (2)

 doi:10.20944/preprints202412.0355.v1

Mint	12 (18)
Goji berries	1 (2)
Charcoal	1 (2)
Linseed oil	1 (2)
Foods (N (%))	
Broccoli	46 (70)
Grapefruit	5 (8)
Garlic	41 (62)
Pomegranate	6 (9)
Oats	13 (20)
Pineapple	20 (30)
Vinegar	28 (42)
Milk	33 (50)
Lemon	34 (52)
Fennel	35 (53)
Papaya	8 (12)
Chilli pepper	24 (36)
Cabbage	35 (53)
Fig	7 (11)
Adverse Events (N (%))	
Nausea	4 (6)
Vomit	2 (3)
Mucositis	2 (3)
Dysgeusia	6 (9)
Constipation	21 (32)
Diarrhea	13 (20)
Headache	8 (12)
Epigastric pain	8 (12)
Asthenia	42 (64)
Skin toxicity	18 (27)
Hand-foot syndrome	4 (6)
Alopecia	9 (14)
Other	2 (3)

Reported side effects were nausea (6%), vomit (3%), asthenia (64%) and constipation (32%). In addition to dexamethasone (14%), for the control of inflammation, and paracetamol (35%) and codeine (8%), for the control of pain, drugs related to the control of nausea and vomiting are taken marginally by patients. The 69% of patients declare that have taken at least one phytotherapeutic product during chemotherapy. The products mainly used are ginger (30%), chamomile (29%), garlic (26%), green tea (26%), soya (18%), mint (18%), aloe (17%), sage (14%), propolis (12%) and turmeric (12%). It was also investigated how patients became aware of herbal products. The interview revealed that under the heading "other" 34.3% of patients became aware of phytotherapeutic substances, 20% through their primary physician while 11.4% thanks to acquaintances.

Considering food, three categories of intake were identified: daily, multi-weekly and monthly. The foods taken by patients are broccoli (70%), garlic (62%), cabbage (53%), fennel (53%), lemon (52%), milk (50%), vinegar (42%), chili pepper (36%) and pineapple (30%). It is interesting to note that, despite numerous recommendations are made about the interactions of grapefruit with drugs, 8% of patients took it.

Evaluating the variables diarrhea, headache and epigastric pain there are statistically significant differences between sexes: men suffer more of diarrhea ($p<0.01$) and headache ($p<0.05$); women suffer more from epigastric pain ($p<0.05$).

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The frequency of side effects during chemotherapy use was showed in Table 2.

Table 2. Frequency of side effects during chemotherapy.

		Percentage of adverse events					
Phytotherapic	**Percentage of assumption**	**Alopecia**	**Epigastric pain**	**Mucositis**	**Hand-foot syndrome**	**Nausea**	**Vomit**
Chamomile	29	73.7	/	68.4	36.8	/	/
Green tea	26	70.6	/	/	/	/	/
Aloe	17	45.5	45.5	/	/	54.6	54.6
Tumeric	12	/	75	/	/	/	/

Considering chamomile, a 2/3 times a week ($p<0.05$) intake has been related to higher levels of mucositis than non-users of the substance. In addition, taking chamomile 2/3 times a week ($p=0.01$) showed a higher incidence of alopecia than those who did not use it. By analyzing green tea, it was found that its consumption 2/3 times a week ($p<0.01$) and 2 times a month ($p<0.001$) was associated with higher alopecia levels than non-use. From the data collected it turned out that those who took aloe daily presented more vomit and nausea compared to those who did not consume it ($p<0,001$). Eventually, taking turmeric 2/3 times a week is related to higher levels of epigastric pain than not taking it ($p<0.01$). Those who took ginger 2/3 times a week seemed to have a lower level of asthenia than those who did not take it ($p<0.05$). Patients who used garlic daily had lower levels of asthenia than those who did not use it ($p=0.001$). The frequency of side effects during selected food assumption was showed in Table 3.

Table 3. Frequency of side effects during selected food assumption.

		Percentage of adverse events						
Food	**Percentage of assumption**	**Epigastric pain**	**Alopecia**	**Dysgeusia**	**Nausea**	**Skin toxicity**	**Vomit**	**Headache**
Fennel	53	25.7	25.7	54.3	25.7	54.3	25.7	/
Cabbage	53	100	62.9	51.4	/	/	/	/
Milk	50	/	/	81.4	/	/	/	/
Chilli pepper	30	/	/	/	/	/	/	79.2
Pineapple	30	/	/	/	65	/	/	/
Oats	20	38.5	38.5	/	/	38.5	/	/
Papaya	12	50	100	/	/	/	/	/

It should be noted that a consumption 2/3 times a week of cabbage is associated with a higher level of dysgeusia ($p<0.01$) and alopecia ($p<0.001$) than those who have not used it. Cabbage consumption at any frequency was more associated with the incidence of epigastric pain than non-use of food ($p<0.05$). Skin toxicity and dysgeusia were more pronounced in patients who consumed fennel 2/3 times a week than those not using the food ($p<0.05$). Daily milk consumers had more dysgeusia than those who did not used it ($p<0.01$). It can be noted that the use of 2/3 times a week and 2 times a month of chili is more associated with headache than not eating the food ($p<0.001$). Considering the variable pineapple, a greater incidence of nausea was observed in those who have used it 2 times a month than those who have not used it ($p<0.01$).

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4. Discussion

The first objective of our study was to identify what phytotherapeutic substances/foods were took by a group of patients with LC undergoing oral chemotherapy. The results showed that the phytotherapics mainly used were ginger, chamomile, garlic and green tea. Analyzing the variability of adverse effects between men and women resulted those men suffered more of diarrhea ($p<0,01$) and headache ($p<0,05$) and women suffered more from epigastric pain ($p<0,05$). In the literature it has been seen how gastric problems have detected significant gender differences, while women are more likely to present constipation problems, men are more affected by diarrhea. The reasons for this seem to be attributed to a different expression of the receptors for the neurotransmitter serotonin (5-HT) responsible for nociception and motility in the stomach. It has also been shown that the administration of antidiarrheal antagonist drugs of serotonin 5-HT3 receptors had a better efficacy in the female sex and at lower dosages [10]. Considering headache, data collected by our study deviates from the evidence. The literature agrees that in all age group women are subject to a higher incidence of headaches than men [11–13]. This may be due to the different expression of sex hormones between woman and man, in particular estrogenic hormones [14,15]. Probably, the reason for the discordance of our results is due to the limited number of women included in the study.

We observed that women suffered most from epigastric pain and the results agree with the literature. In the evidences, the reasons for this sex difference are attributable to several factors including sex hormones: estrogen and progesterone, who affect gastric motility by delaying intestinal emptying, causing epigastric pain. In addition, gastric motility and intestinal emptying, as the sensation of appetite, seem to be influenced by the common anxiety syndromes in women, and by the hormone ghrelin [16–18].

Matricaria chamomilla essential oils and extracts showed interesting antioxidant, antibacterial, antifungal, anticancer, antidiabetic, antiparasitic, anti-inflammatory, anti-depressant, anti-pyretic, anti-allergic and analgesic activities. The anticancer properties of M. chamomilla appear to be linked to apoptosis and necrosis, as well as to a decrease in migration and invasion capacities of oncogenic cells [19]. Chamomile is one of the most widely used substances by cancer patients and one of the most widely used beverages in the world. It is mainly used to reduce chemo-induced neuropathy and mucositis caused by radiotherapy and chemotherapy [20,21]. The application of topical chamomile in the preventive/ therapeutic of chemo-induced oral mucositis seems to be recommended [22]. Chamomile was significantly effective for reducing the frequency of vomiting in cases undergoing chemotherapy for breast cancer [23]. Our work showed that 2/3 times a week intake of chamomile found higher levels of mucositis ($p<0,05$) and alopecia ($p=0,01$) than non-users of the substance, in contrasts with the literature. Given the great biodiversity present among the various species of chamomile plants further studies are necessary in order to be able to recommend the assumption [20,21].

Green tea is produced by processing leaves of the plant Camellia sinensis and is popularly consumed worldwide. Green tea has been shown to have beneficial effects on human health such as anti-cancer, anti-inflammatory, anti-obesity, anti-diabetic, anti-cardiovascular, anti-infectious and anti-neurodegenerative effects. Among the biologically active compounds contained in C. sinesis, the main antioxidant agents are catechins. Epigallocatechin gallate (EGCG) is the most abundant catechin in green tea and believed to be mostly responsible for these biological effects. EGCG is a prominent antioxidant and quenches reactive oxygen species (ROS), which facilitate oxidative DNA damage, mutagenesis, and tumor promotion, leading to its anti-cancer effects [24–26]. Green tea catechins are widely described to be efficient in the prevention of LC [25]. EGCG inhibits LC cell proliferation and promotes apoptosis, agenesis, and epithelial-mesenchymal transition. In addition, EGCG sensitizes LC cells to cisplatin and tyrosine kinase inhibitors [27]. There are few reports on toxicological studies of green tea, mainly related to hepatotoxicity and cytotoxicity [26]. In a phase I trial of patients with locally advanced stage III NSCLC who received chemotherapy (cisplatin and etoposide) and radiation, oral administration of EGCG did not cause dose-limiting toxicities and could reduce the pain score of patients [27]. Analyzing green tea, it was found that a consumption of 2/3 times a week ($p<0,01$) and 2 times a month ($p<0,001$) was associated with higher alopecia levels than non-use.

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Aloe is a medicinal plant known to have antimicrobial, antiviral, anticancer, antioxidant, anti-inflammatory, skin protective, wound healing, and blood glucose and cholesterol regulating properties [28,29]. Aloe seems to act against many types of cancer, such as LCs, lung squamous carcinoma, lung carcinoma, non-small cell lung carcinoma and lung adenocarcinoma [29]. Aloe emodin, an anthraquinone derivative, is a natural compound found in the roots and rhizomes of many plants. This compound has proven its antineoplastic, anti-inflammatory, antiangiogenic, and antiproliferative potential as well as ability to prevent cancer metastasis and potential in reversing multidrug resistance of cancer cells [30,31]. Aloe-emodin enhances the activities of tamoxifen, cisplatin, doxorubicin, cyclophosphamide and 5-fluorouracil and Aloe Vera acts synergistically with cisplatin to inhibit proliferation of human breast and cervical cancer cells. Furthermore, some specific compounds extract from the leaf of Aloe Vera, such as Aloe-emodin, possess higher binding affinity toward estrogen alpha receptor than standard tamoxifen [29].

From the data collected it results that those who took aloe daily presented more vomit and nausea compared to those who did not consume it ($p<0,001$). It is possible that the enhanced activity of chemotherapeutic drugs given by aloe may also increase the toxic effects of the chemotherapy. Studies focusing on aloe emodin have demonstrated its antitumor mechanism, but its toxicity, pharmacokinetics, and pharmaceutical properties are generally not emphasized. Although there is limited data on its toxicity, more research is required [30].

Curcumin, the active ingredient of the Curcuma longa plant, has received great attention over the past two decades as an antioxidant, anti-inflammatory, and anticancer agent. The main mechanisms of action by which curcumin exhibits its unique anticancer activity include inducing apoptosis and inhibiting proliferation and invasion of tumors by suppressing a variety of cellular signaling pathways. Several studies reported curcumin antitumor activity on LC showing its capability to target cancer cell lines [32–34]. Numerous studies have shown that curcumin delays the initiation and progression of NSCLC by affecting a wide range of molecular targets and cell signaling pathways [35]. However, curcumin is not immune from side effects, such as nausea, diarrhea, headache, and yellow stool [33]. We reported that taking turmeric 2/3 times a week is related to higher levels of epigastric pain than not taking it ($p<0,01$). Further studies and clinical trials in humans are needed to validate curcumin as an effective anticancer agent [33].

Ginger (Zingiber Officinale Roscoe) is rich in a variety of components including phenolic compounds, polysaccharides, terpenes, lipids, and organic acids. They have various biological properties that are antioxidant, anti-inflammatory, antimicrobial, anticancer, neuroprotective, antidepressant and antiemetic [36–39]. Nausea and vomiting are the most common and distressing side effects of chemotherapy [37,40,41]. Ginger is one of the most used adjunct treatments for patients with chemotherapy-induced nausea and vomiting (CINV) [37]. Ginger was significantly effective for reducing the frequency of nausea and vomiting in cases undergoing chemotherapy for breast cancer [23,38]. Xiangfeng et al. showed that use of ginger as an adjuvant drug to standard antiemetic therapy produced no additional efficacy in ameliorating the incidence and severity of CINV, in patients with LC receiving cisplatin-based regimens [40]. Furthermore, a clinical trial revealed that ginger can enhance the quality of life of chemotherapy patients by reducing fatigue by up to 80% [41]. Those who took ginger 2/3 times a week had a lower level of asthenia than those who did not take it ($p<0,05$).

Several recent studies have reported numerous health benefits of garlic (Allium sativum), including antitumor, anti-inflammatory, antiangiogenic, antidiabetic, antiarthritic, antihyperglycemic, anticoagulant, antispasmodic, antihistaminic, antibacterial, antiviral, antifungal and antiparasitic effects [42–44]. The anticancer mechanisms of action of garlic-derived phytochemicals include altering mitochondrial permeability, inhibiting angiogenesis, enhancing antioxidative and proapoptotic properties, and regulating cell proliferation [42]. Allicin, a volatile compound found in garlic, decreased the cell viability, proliferation, and migration of NSCLC cells [43]. In our cohort, garlic daily used was related to lower levels of asthenia ($p=0,001$).

Dietary isothiocyanates (ITCs) are the breakdown products of glucosinolates (previously known as thioglucosides), which occur almost exclusively in cruciferous vegetables [45]. ITCs found in cruciferous vegetables were reported to have potent cancer-prevention activities. The best

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characterized ITC is sulforaphane (SFN) [46]. SFN belongs to the active class of isothiocyanates capable of delivering various biological benefits for health promotion and disease prevention. Various studies have proven its beneficial effects against cancer prevention and its possible utilization as a therapeutic agent in cancer treatment [47]. SFN inhibits the proliferation of LC cells and self-renewal of LC stem cells simultaneously [48]. Here, we observed that a consumption 2/3 times a week of cabbage is associated with a higher level of dysgeusia ($p<0,01$) and alopecia ($p<0,001$). Cabbage consumption at any frequency was more associated with the incidence of epigastric pain than non-use of food ($p<0,05$).

Fennel (Foeniculum vulgare) is a perennial aromatic herb [49]. Scopoletin is a natural anticarcinogenic and antiviral coumarin component, isolated from fennel, which leads to apoptosis and to the proliferation inhibition of NSCLC [50]. In a study F. vulgare seed extract, a significantly reduced LC cell growth in vitro and in vivo inducing apoptosis was observed [51]. In our analysis, skin toxicity and dysgeusia were more pronounced in patients who consumed fennel 2/3 times a week ($p<0,05$).

The influence of milk on the development of various types of cancer and, in particular, its often-protective effects have been shown both in vitro and in vivo and in the evaluation of large-scale cohort and case-control studies [52]. Consumption of milk and dairy products probably protects against colorectal cancer, bladder cancer, gastric cancer, and breast cancer. Dairy intake does not seem to be associated with risk of pancreatic cancer, ovarian cancer, or LC, whereas the evidence for prostate cancer risk is inconsistent [53]. In our cohort, daily milk consumers had more dysgeusia than those who did not used it ($p<0,01$).

The habitual consumption of spicy foods was inversely associated with total and certain cause-specific mortality (cancer, ischemic heart diseases, and respiratory diseases), independent of other risk factors of death [54]. Chili pepper (Capsicum annuum) is a prominent cultivated horticultural crop that is traditionally used for food seasoning and is applied for the treatment and prevention of multiple diseases. Its beneficial health properties are due to its abundance and variety of bioactive components, such as carotenoids, capsaicinoids and vitamins. The cytotoxic, genotoxic and antiproliferative effects of carotenoids in tumoral cells can be explained through diverse biological processes. Carotenoids can cause a pro-oxidative effect exclusively on cancer cells, generating and increasing the levels of ROS accumulation as a key method of cancer cell selectively killing [55]. Capsaicin is a hydrophobic, lipophilic vanilloid phytochemical abundantly found in chili peppers and pepper extracts. Several convergent studies show that capsaicin displays robust cancer activity, suppressing the growth, the angiogenesis, and the malignant evolution of several human cancers [56]. Capsaicin can act as a cancer preventive agent and shows wide applications against various types of cancer [57]. Analyzing our data, it can be noted that the use of 2/3 times a week and 2 times a month of chili is more associated with headache ($p<0,001$).

Bromelain is the general term used for a group of proteolytic enzymes that are commonly associated with more specific endopeptidases present in the tissue of the Bromeliaceous plant family. The most prominent plant belonging to this family is the pineapple (Ananas comosus). Various in vivo and in vitro studies have shown that bromelain has antiedematous, anti-inflammatory, anticancer, antithrombotic and fibrinolytic properties, and it facilitate the death of apoptotic cells [58–60]. Bromelain, papain and chymotrypsin are proteolytic enzymes. They can be found in fruits such as pineapple or papaya. Besides their enzymatic function, they are said to reduce side-effects and even to improve the outcome of cancer therapies [61]. The therapeutic potential of bromelain has been investigated at molecular levels in many in vitro and in vivo cancer models involving breast cancer, ovarian, lung, melanoma, digestive system cancer, and leukemia [62]. Considering pineapple, a greater incidence of nausea was observed in those who used it 2 times a month ($p<0,01$).

For some phytotherapics there are evidences that they are effective in the field of oncology. However, this study seems to suggest that their use concomitant with oral chemotherapy may increase the toxicity of chemotherapeutic drugs. It is important that nurses, physicians and pharmacologists carefully evaluate the products that are taken by patients at home, not only focusing on drugs, but also going to investigate the intake of herbal products and foods. To date, there are few

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studies that have certified a clinical significance of phytotherapeutic substances in oncology. Further research is needed to evaluate the interactions between phytotherapeutic products, foods and chemotherapies.

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References

1. International Agency for research on cancer. Global cancer observatory: cancer today. Available online: https://gco.iarc.fr/today/home (accessed on 08/11/2023).
2. Boland, J.M. What's new in benign lung tumours? Histopathology 2024, 84, 124-135, doi:10.1111/his.15037.
3. Stapelfeld, C.; Dammann, C.; Maser, E. Sex-specificity in lung cancer risk. Int J Cancer 2020, 146, 2376-2382, doi:10.1002/ijc.32716.
4. Collado-Borrell, R.; Escudero-Vilaplana, V.; Romero-Jiménez, R.; Iglesias-Peinado, I.; Herranz-Alonso, A.; Sanjurjo-Sáez, M. Oral antineoplastic agent interactions with medicinal plants and food: an issue to take into account. J Cancer Res Clin Oncol 2016, 142, 2319-2330, doi:10.1007/s00432-016-2190-8.
5. Santana Martínez, S.; Marcos Rodríguez, J.A.; Romero Carreño, E. [Oral chemotherapy: food-drug interactions]. Farm Hosp 2015, 39, 203-209, doi:10.7399/fh.2015.39.4.8883.
6. Cheng, Y.Y.; Hsieh, C.H.; Tsai, T.H. Concurrent administration of anticancer chemotherapy drug and herbal medicine on the perspective of pharmacokinetics. J Food Drug Anal 2018, 26, S88-S95, doi:10.1016/j.jfda.2018.01.003.
7. Engdal, S.; Klepp, O.; Nilsen, O.G. Identification and exploration of herb-drug combinations used by cancer patients. Integr Cancer Ther 2009, 8, 29-36, doi:10.1177/1534735408330202.
8. Oken, M.M.; Creech, R.H.; Tormey, D.C.; Horton, J.; Davis, T.E.; McFadden, E.T.; Carbone, P.P. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982, 5, 649-655.
9. Basch, E.; Reeve, B.B.; Mitchell, S.A.; Clauser, S.B.; Minasian, L.M.; Dueck, A.C.; Mendoza, T.R.; Hay, J.; Atkinson, T.M.; Abernethy, A.P.; et al. Development of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). J Natl Cancer Inst 2014, 106, doi:10.1093/jnci/dju244.
10. Katsumata, R.; Shiotani, A.; Murao, T.; Ishii, M.; Fujita, M.; Matsumoto, H.; Haruma, K. Gender Differences in Serotonin Signaling in Patients with Diarrhea-predominant Irritable Bowel Syndrome. Intern Med 2017, 56, 993-999, doi:10.2169/internalmedicine.56.7674.
11. VanderPluym, J.H.; Charleston, L.; Stitzer, M.E.; Flippen, C.C.; Armand, C.E.; Kiarashi, J. A Review of Underserved and Vulnerable Populations in Headache Medicine in the United States: Challenges and Opportunities. Curr Pain Headache Rep 2022, 26, 415-422, doi:10.1007/s11916-022-01042-w.
12. Ackley, E.; Halker Singh, R.B. Sex and gender: Opportunities to expand research and understanding within headache medicine. Headache 2022, 62, 771-773, doi:10.1111/head.14351.
13. Fitzgerald, M.C.; Saelzler, U.G.; Panizzon, M.S. Sex Differences in Migraine: A Twin Study. Front Pain Res (Lausanne) 2021, 2, 766718, doi:10.3389/fpain.2021.766718.
14. Delaruelle, Z.; Ivanova, T.A.; Khan, S.; Negro, A.; Ornello, R.; Raffaelli, B.; Terrin, A.; Mitsikostas, D.D.; Reuter, U.; (EHF-SAS), E.H.F.S.o.A.S. Male and female sex hormones in primary headaches. J Headache Pain 2018, 19, 117, doi:10.1186/s10194-018-0922-7.
15. Reddy, N.; Desai, M.N.; Schoenbrunner, A.; Schneeberger, S.; Janis, J.E. The complex relationship between estrogen and migraines: a scoping review. Syst Rev 2021, 10, 72, doi:10.1186/s13643-021-01618-4.
16. StatPearls. 2023.
17. Lichtman, J.H.; Leifheit, E.C.; Safdar, B.; Bao, H.; Krumholz, H.M.; Lorenze, N.P.; Daneshvar, M.; Spertus, J.A.; D'Onofrio, G. Sex Differences in the Presentation and Perception of Symptoms Among Young Patients With Myocardial Infarction: Evidence from the VIRGO Study (Variation in Recovery: Role of Gender on

 doi:10.20944/preprints202412.0355.v1

Outcomes of Young AMI Patients). Circulation 2018, 137, 781-790, doi:10.1161/CIRCULATIONAHA.117.031650.
18. Choi, Y.J.; Park, Y.S.; Kim, N.; Kim, Y.S.; Lee, S.M.; Lee, D.H.; Jung, H.C. Gender differences in ghrelin, nociception genes, psychological factors and quality of life in functional dyspepsia. World J Gastroenterol 2017, 23, 8053-8061, doi:10.3748/wjg.v23.i45.8053.
19. El Mihyaoui, A.; Esteves da Silva, J.C.G.; Charfi, S.; Candela Castillo, M.E.; Lamarti, A.; Arnao, M.B. Chamomile (Life (Basel) 2022, 12, doi:10.3390/life12040479.
20. Oveissi, V.; Ram, M.; Bahramsoltani, R.; Ebrahimi, F.; Rahimi, R.; Naseri, R.; Belwal, T.; Devkota, H.P.; Abbasabadi, Z.; Farzaei, M.H. Medicinal plants and their isolated phytochemicals for the management of chemotherapy-induced neuropathy: therapeutic targets and clinical perspective. Daru 2019, 27, 389-406, doi:10.1007/s40199-019-00255-6.
21. Salehi, B.; Lopez-Jornet, P.; Pons-Fuster López, E.; Calina, D.; Sharifi-Rad, M.; Ramírez-Alarcón, K.; Forman, K.; Fernández, M.; Martorell, M.; Setzer, W.N.; et al. Plant-Derived Bioactives in Oral Mucosal Lesions: A Key Emphasis to Curcumin, Lycopene, Chamomile,. Biomolecules 2019, 9, doi:10.3390/biom9030106.
22. de Lima Dantas, J.B.; Freire, T.F.C.; Sanches, A.C.B.; Julião, E.L.D.; Medrado, A.R.A.P.; Martins, G.B. Action of Matricaria recutita (chamomile) in the management of radiochemotherapy oral mucositis: A systematic review. Phytother Res 2022, 36, 1115-1125, doi:10.1002/ptr.7378.
23. Sanaati, F.; Najafi, S.; Kashaninia, Z.; Sadeghi, M. Effect of Ginger and Chamomile on Nausea and Vomiting Caused by Chemotherapy in Iranian Women with Breast Cancer. Asian Pac J Cancer Prev 2016, 17, 4125-4129.
24. Hayakawa, S.; Ohishi, T.; Miyoshi, N.; Oishi, Y.; Nakamura, Y.; Isemura, M. Anti-Cancer Effects of Green Tea Epigallocatchin-3-Gallate and Coffee Chlorogenic Acid. Molecules 2020, 25, doi:10.3390/molecules25194553.
25. Musial, C.; Kuban-Jankowska, A.; Gorska-Ponikowska, M. Beneficial Properties of Green Tea Catechins. Int J Mol Sci 2020, 21, doi:10.3390/ijms21051744.
26. Zhao, T.; Li, C.; Wang, S.; Song, X. Green Tea (Molecules 2022, 27, doi:10.3390/molecules27123909.
27. Zhang, L.; Wen, J.X.; Hai, L.; Wang, Y.F.; Yan, L.; Gao, W.H.; Hu, Z.D.; Wang, Y.J. Preventive and therapeutic effects of green tea on lung cancer: a narrative review of evidence from clinical and basic research. J Thorac Dis 2022, 14, 5029-5038, doi:10.21037/jtd-22-1791.
28. Sánchez, M.; González-Burgos, E.; Iglesias, I.; Gómez-Serranillos, M.P. Pharmacological Update Properties of. Molecules 2020, 25, doi:10.3390/molecules25061324.
29. Manirakiza, A.; Irakoze, L.; Manirakiza, S. Aloe and its Effects on Cancer: A Narrative Literature Review. East Afr Health Res J 2021, 5, 1-16, doi:10.24248/eahrj.v5i1.645.
30. Şeker Karatoprak, G.; Küpeli Akkol, E.; Yücel, Ç.; Bahadır Acıkara, Ö.; Sobarzo-Sánchez, E. Advances in Understanding the Role of Aloe Emodin and Targeted Drug Delivery Systems in Cancer. Oxid Med Cell Longev 2022, 2022, 7928200, doi:10.1155/2022/7928200.
31. Zhang, Q.; Chen, W.W.; Sun, X.; Qian, D.; Tang, D.D.; Zhang, L.L.; Li, M.Y.; Wang, L.Y.; Wu, C.J.; Peng, W. The versatile emodin: A natural easily acquired anthraquinone possesses promising anticancer properties against a variety of cancers. Int J Biol Sci 2022, 18, 3498-3527, doi:10.7150/ijbs.70447.
32. Tomeh, M.A.; Hadianamrei, R.; Zhao, X. A Review of Curcumin and Its Derivatives as Anticancer Agents. Int J Mol Sci 2019, 20, doi:10.3390/ijms20051033.
33. Giordano, A.; Tommonaro, G. Curcumin and Cancer. Nutrients 2019, 11, doi:10.3390/nu11102376.
34. Wan Mohd Tajuddin, W.N.B.; Lajis, N.H.; Abas, F.; Othman, I.; Naidu, R. Mechanistic Understanding of Curcumin's Therapeutic Effects in Lung Cancer. Nutrients 2019, 11, doi:10.3390/nu11122989.
35. Salehi, M.; Movahedpour, A.; Tayarani, A.; Shabaninejad, Z.; Pourhanifeh, M.H.; Mortezapour, E.; Nickdasti, A.; Mottaghi, R.; Davoodabadi, A.; Khan, H.; et al. Therapeutic potentials of curcumin in the treatment of non-small-cell lung carcinoma. Phytother Res 2020, 34, 2557-2576, doi:10.1002/ptr.6704.
36. Mahomoodally, M.F.; Aumeeruddy, M.Z.; Rengasamy, K.R.R.; Roshan, S.; Hammad, S.; Pandohee, J.; Hu, X.; Zengin, G. Ginger and its active compounds in cancer therapy: From folk uses to nano-therapeutic applications. Semin Cancer Biol 2021, 69, 140-149, doi:10.1016/j.semcancer.2019.08.009.
37. Choi, J.; Lee, J.; Kim, K.; Choi, H.K.; Lee, S.A.; Lee, H.J. Effects of Ginger Intake on Chemotherapy-Induced Nausea and Vomiting: A Systematic Review of Randomized Clinical Trials. Nutrients 2022, 14, doi:10.3390/nu14234982.
38. Kim, S.D.; Kwag, E.B.; Yang, M.X.; Yoo, H.S. Efficacy and Safety of Ginger on the Side Effects of Chemotherapy in Breast Cancer Patients: Systematic Review and Meta-Analysis. Int J Mol Sci 2022, 23, doi:10.3390/ijms231911267.

39. de Lima, R.M.T.; Dos Reis, A.C.; de Menezes, A.P.M.; Santos, J.V.O.; Filho, J.W.G.O.; Ferreira, J.R.O.; de Alencar, M.V.O.B.; da Mata, A.M.O.F.; Khan, I.N.; Islam, A.; et al. Protective and therapeutic potential of ginger (Zingiber officinale) extract and [6]-gingerol in cancer: A comprehensive review. Phytother Res 2018, 32, 1885-1907, doi:10.1002/ptr.6134.
40. Li, X.; Qin, Y.; Liu, W.; Zhou, X.Y.; Li, Y.N.; Wang, L.Y. Efficacy of Ginger in Ameliorating Acute and Delayed Chemotherapy-Induced Nausea and Vomiting Among Patients With Lung Cancer Receiving Cisplatin-Based Regimens: A Randomized Controlled Trial. Integr Cancer Ther 2018, 17, 747-754, doi:10.1177/1534735417753541.
41. da Silva, R.L.M.; da Silva, T.T.M.; Pessoa, R.L.; Sarmento, A.C.A.; Medeiros, K.S.; Dantas, D.V.; Dantas, R.A.N. Use of ginger to control nausea and vomiting caused by chemotherapy in patients with cervical cancer undergoing treatment: An experiment. Medicine (Baltimore) 2022, 101, e29403, doi:10.1097/MD.0000000000029403.
42. De Greef, D.; Barton, E.M.; Sandberg, E.N.; Croley, C.R.; Pumarol, J.; Wong, T.L.; Das, N.; Bishayee, A. Anticancer potential of garlic and its bioactive constituents: A systematic and comprehensive review. Semin Cancer Biol 2021, 73, 219-264, doi:10.1016/j.semcancer.2020.11.020.
43. Mondal, A.; Banerjee, S.; Bose, S.; Mazumder, S.; Haber, R.A.; Farzaei, M.H.; Bishayee, A. Garlic constituents for cancer prevention and therapy: From phytochemistry to novel formulations. Pharmacol Res 2022, 175, 105837, doi:10.1016/j.phrs.2021.105837.
44. Zhang, Y.; Liu, X.; Ruan, J.; Zhuang, X.; Zhang, X.; Li, Z. Phytochemicals of garlic: Promising candidates for cancer therapy. Biomed Pharmacother 2020, 123, 109730, doi:10.1016/j.biopha.2019.109730.
45. Na, G.; He, C.; Zhang, S.; Tian, S.; Bao, Y.; Shan, Y. Dietary Isothiocyanates: Novel Insights into the Potential for Cancer Prevention and Therapy. Int J Mol Sci 2023, 24, doi:10.3390/ijms24031962.
46. Elkashty, O.A.; Tran, S.D. Sulforaphane as a Promising Natural Molecule for Cancer Prevention and Treatment. Curr Med Sci 2021, 41, 250-269, doi:10.1007/s11596-021-2341-2.
47. Iahtisham-Ul-Haq; Khan, S.; Awan, K.A.; Iqbal, M.J. Sulforaphane as a potential remedy against cancer: Comprehensive mechanistic review. J Food Biochem 2022, 46, e13886, doi:10.1111/jfbc.13886.
48. Wang, F.; Sun, Y.; Huang, X.; Qiao, C.; Zhang, W.; Liu, P.; Wang, M. Sulforaphane inhibits self-renewal of lung cancer stem cells through the modulation of sonic Hedgehog signaling pathway and polyhomeotic homolog 3. AMB Express 2021, 11, 121, doi:10.1186/s13568-021-01281-x.
49. Uusitalo, L.; Salmenhaara, M.; Isoniemi, M.; Garcia-Alvarez, A.; Serra-Majem, L.; Ribas-Barba, L.; Finglas, P.; Plumb, J.; Tuominen, P.; Savela, K.; et al. Intake of selected bioactive compounds from plant food supplements containing fennel (Foeniculum vulgare) among Finnish consumers. Food Chem 2016, 194, 619-625, doi:10.1016/j.foodchem.2015.08.057.
50. Yuan, C.; Wang, M.H.; Wang, F.; Chen, P.Y.; Ke, X.G.; Yu, B.; Yang, Y.F.; You, P.T.; Wu, H.Z. Network pharmacology and molecular docking reveal the mechanism of Scopoletin against non-small cell lung cancer. Life Sci 2021, 270, 119105, doi:10.1016/j.lfs.2021.119105.
51. Ke, W.; Zhao, X.; Lu, Z. Foeniculum vulgare seed extract induces apoptosis in lung cancer cells partly through the down-regulation of Bcl-2. Biomed Pharmacother 2021, 135, 111213, doi:10.1016/j.biopha.2020.111213.
52. Leischner, C.; Egert, S.; Burkard, M.; Venturelli, S. Potential Protective Protein Components of Cow's Milk against Certain Tumor Entities. Nutrients 2021, 13, doi:10.3390/nu13061974.
53. Thorning, T.K.; Raben, A.; Tholstrup, T.; Soedamah-Muthu, S.S.; Givens, I.; Astrup, A. Milk and dairy products: good or bad for human health? An assessment of the totality of scientific evidence. Food Nutr Res 2016, 60, 32527, doi:10.3402/fnr.v60.32527.
54. Jiang, T.A. Health Benefits of Culinary Herbs and Spices. J AOAC Int 2019, 102, 395-411, doi:10.5740/jaoacint.18-0418.
55. Villa-Rivera, M.G.; Ochoa-Alejo, N. Chili Pepper Carotenoids: Nutraceutical Properties and Mechanisms of Action. Molecules 2020, 25, doi:10.3390/molecules25235573.
56. Merritt, J.C.; Richbart, S.D.; Moles, E.G.; Cox, A.J.; Brown, K.C.; Miles, S.L.; Finch, P.T.; Hess, J.A.; Tirona, M.T.; Valentovic, M.A.; et al. Anti-cancer activity of sustained release capsaicin formulations. Pharmacol Ther 2022, 238, 108177, doi:10.1016/j.pharmthera.2022.108177.
57. Chapa-Oliver, A.M.; Mejía-Teniente, L. Capsaicin: From Plants to a Cancer-Suppressing Agent. Molecules 2016, 21, doi:10.3390/molecules21080931.
58. Varilla, C.; Marcone, M.; Paiva, L.; Baptista, J. Bromelain, a Group of Pineapple Proteolytic Complex Enzymes (Foods 2021, 10, doi:10.3390/foods10102249.
59. Agrawal, P.; Nikhade, P.; Patel, A.; Mankar, N.; Sedani, S. Bromelain: A Potent Phytomedicine. Cureus 2022, 14, e27876, doi:10.7759/cureus.27876.
60. Chakraborty, A.J.; Mitra, S.; Tallei, T.E.; Tareq, A.M.; Nainu, F.; Cicia, D.; Dhama, K.; Emran, T.B.; Simal-Gandara, J.; Capasso, R. Bromelain a Potential Bioactive Compound: A Comprehensive Overview from a Pharmacological Perspective. Life (Basel) 2021, 11, doi:10.3390/life11040317.

 doi:10.20944/preprints202412.0355.v1

61. Gremmler, L.; Kutschan, S.; Dörfler, J.; Büntzel, J.; Hübner, J. Proteolytic Enzyme Therapy in Complementary Oncology: A Systematic Review. Anticancer Res 2021, 41, 3213-3232, doi:10.21873/anticanres.15108.
62. Hikisz, P.; Bernasinska-Slomczewska, J. Beneficial Properties of Bromelain. Nutrients 2021, 13, doi:10.3390/nu13124313.