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Herb-Drug Interactions in Oncology: A Clinical Up-Date

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Abstract

Phytotherapy, which is defined as the use of titrated herbal extracts in clinical practice, has been receiving increasing interest in the scientific community recently. In the present report, information regarding the most important mechanisms underlying the drug-drug interactions (DDI) and herb-drug interactions (HDI) has been discussed briefly. Furthermore, the best known and relevant interactions of *Ginkgo biloba*, *Citrus paradisi* (Grapefruit Juice), *Silybum marianum* (Milk Thistle), *Hypericum perforatum* (St. John Wort) and *Camellia sinensis* (Green Tea) that have emerged from clinical evidence have been listed. The last part of the present report has been dedicated to cancer patients, with a summary of interactions between plants and drugs/chemotherapeutics. The "Reversed Grading for clinical risk of interactions in oncology", a tool conceived by the Tuscan Network of Integrative Medicine, has also been reported.

Keywords
Clinical phytotherapy; herb-drug interactions; chemotherapy

1. Introduction

In the last few years, increasing interest in the perceived use of herbal medicines (HMs) as a complementary and/or alternative way to cure diseases has developed in the scientific community. The assumption that herbal medicines are safe and not involved in any kind of interaction with drugs is quite common among the consumers, and rather surprisingly, among the healthcare providers as well. However, a wide range of studies in the literature clearly demonstrates the possibility of herbs being dangerous when used as self-medication or without adequate pharmacological knowledge, especially in frail patients (e.g., cancer patients) and in combination with various drugs.

Every medicinal plant contains several hundreds of chemical substancesthatinteract with each other as well as with synthetic drugs. The risks associated with herbs are lowered when used in the form of standardized and purified herbal extracts as well as in case of prescription by physicians experienced in clinical phytotherapy.

Pre-clinical data are largely present, while clinical evidence islimited, and at certain times, inconclusive.Moreover, "clinical" evidence should *not* be extrapolated as a direct consequence of "pre-clinical" evidence. Therefore, published studies with clinicalevidenceon herb-drug interactions are currently the most important databases in this area of study.

2. Herb–Drug Interactions

Herbal extracts (HEs) contain chemicals derived from different parts of the plants (such as seeds, leaves, roots, flowers, etc.) or from a mixtures of the whole plant, too. These chemicals are metabolized and cleared from the human body through the same metabolic pathways that eliminatesynthetic drugs and other substances. Therefore, it is argued that pharmacokinetic (PK) herb-drug interactions may develop.

The assessment of drug-drug interactions (DDI) [1-5] is a part of *in vitro* and *in vivo* investigations; the first one serves to just provide information regarding the path to be undertaken for the deeper subsequent *in vivo* steps.Furthermore, it is difficult to extrapolate the studies conducted on animals to humans because of species differences [6].

Physiologicallybased pharmacokinetic modeling (PBPK) [7] is generally used to direct the *in vivo* DDI trials. However, it is not possible to apply PBPK plainly to herbal medicines (HMs) as certain pre-requisites would be necessary, which are as follows: a) identification of herbal constituent(s) which form(s) the basis of interaction; b) standardized extracts (i.e., titrated in their constituents); c) *in vitro* studies to define the interaction potential; and d) information regarding the bioavailability and human PK of these compounds (PK characteristics, however, are currently only a few in number). Therefore, in the majority of the cases, any extrapolation of the *in vitro* studies does not necessarily predict the outcome of the corresponding *in vivo* studies. Nonetheless, even though limited, this approach may potentially assist in identifying the perpetrator constituents, evaluating the characteristics of these constituents, and finally, in describing the interactions mechanistically [8].

PK involves absorption, distribution, metabolism, and excretion (ADME) pathways. Drug absorption is dependent on intestinal uptake/efflux transporters and intestinal metabolizing enzymes, as metabolism and excretion occur mostly at hepatic and renal sites. Uptake transporters, which deal with absorption and distribution, directly affect the plasma and tissue exposures to drugs [9].

In regard to*metabolic enzymes*, their inhibition increases the victim drug, as a consequence ofdecreased clearance or augmented bioavailability. The most common mechanism inthe case of PK interactions is enzyme inhibition. Enzyme inhibition may be classified into reversible inhibition (competitive or non-competitive) and time-dependent inhibition (TDI); the latter may remain active even after the withdrawal of the perpetrator drug and requires newly operating protein synthesis. The cytochrome P450 (CYP) family, which includes CYP1A2, CYP2B6, CYP3A4, CYP2C8/9/19, and CYP2D6 (the first three being the most investigated ones), is known to be involved in *phase I reactions* (oxidative metabolism)of drugs and herbs. CYP2C and CYP2B families are rarely considered in the studies conducted on herbs. Moreover, the clinical impact of different enzymes may not be the same in terms of inducibility and susceptibility to inhibition. In regard to*phase II reactions* (involvingUDP-glucuronosyltransferase, N-acetyltransferase, etc), it is worth mentioning that studies on these reactions are virtually lacking in the literature, which implies that the potential of herbs to interfere with such mechanisms is completely unknown [10, 11].

In regard to*drugtransporters*,decreased activity (competitive and non-competitive reversible inhibition) or increased expression (induction) has been observed. ATP binding-cassette (ABC) family (including MDR1, better known as P-gp), multidrug resistance-associated proteins (MRPs), and breast cancer resistance protein (BCRP) are able to modulate the efflux of their substrates.In parallel, the solute carrier (SLC) family, such as the organic anion transporting polypeptides, organic anion transporters (OATs), and organic cation transporters (OCTs), affects the uptake mainly, and in different ways, deal with the oral absorption and with the renal and hepatobiliary drug disposition. Clinically, their effects are ultimately expressed as increased or decreased systemic exposure to the drug, depending on the direction of the flux and the transporter localization on the cell [11].

Table 1*(cited completely as a part of the* revisited and updated one from a previous study [27]) summarizes four of the best known and well-studied herbal extracts and products: Ginkgo (*Ginkgo biloba*), Grapefruit juice (*Citrus paradisi*), Milk thistle (*Silybum marianum*), and St. John's wort (*Hypericum perforatum*).

Table 1 Effect of herbal products and extracts and their constituents on metabolic enzymes and transporters**.**

Botanical	**Metabolic enzymes and transporters affected,** based on the data from human studies	**Effects of drug concentration** with published clinical herb-drug interaction
Ginkgo **(*Ginkgo biloba*)** *Flavonoids:* e.g., quercetin, kaempferol *Terpenoids:* ginkgolides A and B, and bilobalide	CYP1A2 (↔); CYP2D6 (↔), CYP2E1 (↔) CYP2C19 (generally ↔, possible ↑) CYP2C9 (generally ↔, possible ↑) CYP3A4 (generally ↔, possible ↑) UGT1A (↓ in vitro) P-gp (generally ↔, possible ↓) OATP (generally ↔, possible ↓)	*Decrease* Plasma level of CYP substrates (midazolam [12], omeprazole [13], tolbutamide [14]) *Increase* Plasma levels of P-gp substrates (talinolol [15,16])
Grapefruit juice ***(Citrus paradisi)*** Flavonoids: naringin, naringenin, quercetin. Furanocoumarins: bergamotin, 6'7'dihydroxybergamottin	CYP3A4 (↓) CYP2D6 (↓) Enteric CYP3A4 (↓) OATP1A2 (↓) OATP2B1 (↓)	*Increase* Plasma level of CYP3A substrates OR *Decrease* Plasma level of OATP substrates *Drug category:* Antihistamines (fexofenadine, terfenadine) Anti-infectives (erythromycin, halofantrine, praziquantel) Antiretrovirals (saquinavir) Cardiovascular drugs (aliskiren, azelnidipine, celiprolol, felodipine, manidipine, nicardipine, nifedipine, nimodipine, nisoldipine, talinolol) Central nervous system agents (alfentanil, buspirone, carbamazepine, diazepam, fluvoxamine, methadone, midazolam, phenytoin, sertraline, triazolam) Immunosuppressants (cyclosporine, tacrolimus) Statins (atorvastatin, lovastatin, simvastatin) Oncology agents (etoposide) [17,18,19]

Milk thistle ***(Silybum marianum)*** Flavonolignans: silybin	CYP2C9 (↓) CYP3A4 (↔, possible ↑) CYP1A2 (↔) CYP2D6 (↔) CYP2E1 (↔) UGT1A1 (↔) OATP1B1 (↔) P-gp (↔, possible↓)	<u>*Increase*</u> Plasma levels (losartan [20] and talinolol [21]) <u>*Decrease*</u> Plasma levels of CYP3A/P-gp substrates (Metronidazole [22])
St. John's wort (*Hypericum perforatum*) *Phloroglucinol:* as hyperforin, Hypercins *Flavonoids:* e.g., quercetin	CYP1A2 (↑) CYP2B6 (↑) CYP2E1 (↑) CYP3A4 (↑) CYP2C9 (↑) CYP2C19 (↑) P-gp (↑)	<u>*Decrease plasma levels of*</u> Antihistamines (e.g., fexofenadine) Antivirals (indinavir, lamivudine, nevirapine) Cardiovascular drugs (digoxin, ivabradine, nifedipine, talinolol, verapamil, warfarin) Central nervous system agents (amitriptyline, alprazolam, buspirone, methadone, midazolam, phenytoin, sertraline) Hypoglycemic agents (gliclazide) Immunosuppressants (cyclosporine, tacrolimus) Statins (atorvastatin, simvastatin) Oncology agents (imatinib, irinotecan) Proton pump inhibitors (omeprazole) H2-Receptor Histamine Antagonist (cimetidine)[23,24,25,26]

Both *in vitro* and *in vivo* studies conducted on Green Tea (*Camellia sinensis*) have suggested that its extracts (especially the constituent epigallocatechin-3-gallate) may inhibit the activity of different drug transporters including OATP1A2, OATP1B1, and OATP2B1 [28,29,30,31].It is also recommended to refer torecent reports [32,33] for further information regarding the interactions of green tea with cardiovascular drugs.

3. Herb-Drug Interactions in Oncology

Cancer is a big threattohumans due to the mortality rate it results in. Aging, as well as soil and air pollution, are considered a relevant part of this problem owing to the epigenetic mechanisms involved [34]. Chemotherapy represents the first line of treatment in cancer, with the aim to kill the cancer cells or inhibit their proliferation. Narrow therapeutic index and wide inter-individual PK variability may lead to high and unpredictable dose-related toxicity as well as a variable anti-tumor response, both of which undermine the effectiveness of this therapy [35]. Moreover, in a study conducted on the residents of Canada and USA, the overall contribution of curative and

adjuvant cytotoxic chemotherapy to five-year survival in adults was estimated to be just a little above 2% [36]. Cancer patients have been reported to be increasingly inclining toward HMs [37,38,39] to improve their health, especially to reduce the side effects of the traditional treatment methods. The risk of interactions exists, and it is necessary to be aware of it so that the symptoms are not erroneously attributed to the chemotherapeutics or to disease progression solely.

The most studied herbal remedies, with documented trials conducted on cancer patients as well, are Ginseng (*Panax ginseng C.A. Meyer*) for the treatment of fatigue [40], Cannabis (*Cannabis sativa*) for pain relief [41], and Ginger (*Zingiber officinale*) to provide relief in case of post-chemotherapy nausea and vomiting [42,43] *(1A Grading)*. *Lavandula officinalis* essential oil may be used as oral and external therapy in case of anxiety [44], while Aloe (*Aloe vera*) may be used for chemotherapy-related mucositis [45] and Saffron (*Crocus sativus*) may be used for mild to moderate depressive syndrome [46] *(1B Grading)*. Similarly, Guaranà (*Paullinia cupana*) may be used for the treatment of fatigue [47], Cannabis may be used to provide relief inpost-chemotherapy nausea and vomiting [48] *(2B Grading)*, and Rhodiola (*Rhodiola rosea*) may be used for mild to moderate depressive syndrome [49] *(2C Grading)*.

Certain medicinal plants, whose pharmacological and clinical activities have been studied extensively, may be used safely even if they have been tested on and documented only forthe non-cancer patients; for example, Boswellia (*Boswellia serrata*) resin [50] and *Ribes nigrum* leaf extracts [51]. The anti-inflammatory properties of these medicinal plants allow them to be used successfully in breast cancer patients for the treatment of muscle and joint pains resulting from anti-cancer therapies.

Pre-clinical studies have demonstrated that certain herbs (e.g., *Curcuma longa* in colorectal cancer [52]) may increase the susceptibility of cancer cells to chemotherapy, lowering the incidence of side effects and ameliorating the quality of life and survival among the patients.On the contrary, it is known that certain other herbs are able to worsen these aspects by reducing the efficacy of the anti-cancer treatments; examples of such herbs include *Hypericum perforatum, Allium sativum*, *G. biloba*, *Echinacea purpurea, Panax ginseng*, etc. [37].

Scientific research has reported the occurrence of Imatinib-related hepatitis in a patient who consumed Ginseng (a P450 inhibitor) [53]. An interaction between Bortezomib and Green Tea [54] has also been reported. It is noteworthy to mention the isoflavonecontaining herbs, such as Soy (*Glycine max*), Hop (*Humulus lupulus*), Red Clover (*Trifolium pratense*), and Sage (*Salvia officinalis*),the extracts of which are often consumed by women as safer alternatives to hormone therapy for the treatment of menopause symptoms. However, the effects of these herbs on the women who are at risk for breast cancer remain largely unknown. Therefore, until the knowledge regarding the exact mechanisms underlying the action of these herbs is unveiled, caution is compulsory and the use of these herbs must be avoided. It is relevant here to refer to a recent study conducted on *Trifolium pratense* (Red Clover) [54].

4. Reversed Grading

In order to improve the clinical interpretation of the *in vitro* and/or *in vivo* interactions between medicinal plants and chemotherapy, the Tuscan Network of Integrative Medicine (now known as the Tuscan Regional Centre for Integrative Medicine) has suggested what is referred to

as"*Reversed Grading*" [56], in which the principal level of evidence corresponds to the main level of the negative recommendation. This classification also allows the possibility of using and exploiting the positive interactions (*synergies*) between medicinal plants and drugs (Table 2). This tool may be considered useful, from a practical point of view, for the doctor, particularly in the management of cancer patients (Table 3).

Table 2 Reversed grading for clinical risk of interactions in oncology (the Tuscan Network of Integrative Medicine).

Reversed Grading	**Evidence**	**Recommendation**
IA	In vitro and in vivo Laboratory evidence and clinical reports on pharmacological interference with a proven risk of effectiveness reduction of anticancer therapy	FORBIDDEN from prescription during oncological therapy
IIA	Only in vitro and in vivo laboratory evidence without any sign of clinic interference, and no research carried out to study the clinical interactions in oncology	Evaluate whether to ABSTAIN or NOT from prescription on the basis of a risk/benefit assessment of therapy. Stop the administration in the presence of reduced effectiveness or ineffectiveness of anti-cancer therapy and/or adverse effects
IIB	Only in vitro and in vivo laboratory evidence, without any sign of clinic interference in spite of the research carried out	PRESCRIPTION and monitoring Stop the administration in the presence of reduced effectiveness or ineffectiveness of anti-cancer therapy and/or adverse effects
IIIB	Only in vitro laboratory evidence (NOT in vivo), without any sign of clinical interference in spite of the research carried out	PRESCRIPTION and monitoring. Stop the administration in the presence of reduced effectiveness or ineffectiveness of anti-cancer therapy and/or adverse effects
IVB	No evidence of negative interference, rather, positive evidence of oncological-therapy potentiation	PRESCRIPTION and monitoring. Report to the referring oncologist for any reformulation in the dose of anti-cancer treatment and/or adverse effects
VB	No evidence of negative interference and positive evidence of oncological therapy potentiation	PRESCRIPTION. Report to the referring oncologist

Table 3 List of medicinal plants,interactions,possible effects and reversed grading in oncology.

Botanical Name	Interactions with	Type	Possible Effects	Reversed Grading
Citrus paradisi (juice)	Chemotherapeutics Anxiolytics Statins	Pharmacokinetic	Drug Toxicity: Fast and long-acting Effect	I A
Hypericum perforatum	Tamoxifen Imatinib Irinotecan Taxol Paclitaxel Etoposide Crizotinib Cyclophosphamide Cyclosporin Everolimus Anesthetics Anticoagulants PPI (Proton Pump Inhibitors) Acetaminophen	Pharmacokinetic	Drug Effectiveness Reduction	I A
	SRI (Serotonin Re-uptake Inhibitors) Trazodone	Pharmacodynamic	Serotoninergic syndrome	
Glycyrrhiza glabra	Cortisones Diuretics Digitalis Others	Pharmacokinetic	Hypokalemia Hypertension	II A
Ginkgo biloba	Antiplatelets Oral Anticoagulants	Pharmacodynamic	Hemorrhagic risk	II A
Panax Ginseng	Irinotecan Taxol Imatinib Oral Anticoagulants Tamoxifen Antihypertensive	Pharmacokinetic	Possible increased KT toxicity (Imatinib) Possible effect: estrogen stimulating Possible Tamoxifen Effectiveness Reduction	II A
Glycine max, Trifolium pratense, Humulus	Tamoxifen Aromatase Inhibitors	Pharmacodynamic	Possible Reduction of Drug Effectiveness	II B

lupulus, and *Salvia officinalis*				
Echinacea spp.	Immunosuppressors Tamoxifen and Irinotecan (in vitro) Etoposide (in vivo)	Pharmacodynamic Pharmacokinetic	Possible Thrombocytopenia etoposide-related	II B
Rhodiola rosea	Antidepressants	Pharmacokinetic		III B
Boswellia serrata	Cortisones	Pharmacodynamic	Anti-edema Ant-inflammatory Synergic effect: cortisones	IIIB
Zingiber officinale	NSAIDs (Nonsteroidal anti-inflammatory drugs) Chemotherapeutics	Pharmacodynamic	Anti-nausea	IV B
Crocus sativus	Antidepressants	Pharmacodynamic	Possible cumulative effects	IV B
Lavandula officinalis	Anxiolytics	Pharmacodynamic	Possible cumulative effects	IV B
Astragalus membranaceus	Chemotherapy	Pharmacodynamic	Possible synergic effect with KTI Colorectal and Lung Cancer	IV B
Aloe spp.	Laxatives Oral Antidiabetics	Pharmacokinetic	Diarrhea Electrolytic impairment Cumulative effects	IV B
Camellia sinensis	Bortezomib Beta-Blockers	Pharmacokinetic	Possible Drug effectiveness Reduction	II B
	Temozolomide	Pharmacokinetic	Possible synergies	IV B
Curcuma longa	Gemcitabine Oxaliplatin	Pharmacokinetic	Cumulative effects No toxicity, side effects, nor negative interferences reported	V B

5. Conclusions

As a first and unique attempt in Italy, efforts were put by the Region of Tuscany for spreadingawareness regarding complementary and integrative medicines (CIM) over the last several years. A team of esteemed physicians has been working hard to share the results acquired in the public hospital facilities with the scientific community [55, 56]. It is important that this work continues so as to improve the efficacy of the acquired results. Research and herbal pharmacovigilance [57] must form the basis for clinical practice and require implementation. It is necessary that all the healthcare providers are informed well regarding this issue on an urgent basis, as it is only through the mutual exchange of skills and ideas that a community grows.

The outpatient departments (OPDs)come in contact with numerous people who are affected by various diseases, ranging from minor illnesses to major health issues such as cancer. At certain times, clinical phytotherapy may be resolutory, while at other times, it may just serve as a support to the “conventional” drugs and treatment methods.

The compelling evidence of a suitable treatment which would translate into patients' health is the accurate updated knowledge regarding herbs and herb-drug interactions obtained from research studies. The information provided in the present brief review is just a small portion of a complex issue that requires more than just a few lines or pages of description.The ellipsis is required to be filled with detailed answers;we owe them to our patients.

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Author Contribution

All research done by the authors. *Francesco Sivelli* conceived, designed, participated in the research and wrote the article; *Elio Rossi* and *Mariella Di Stefano* participated in the research and in the writing of the article; *Sonia Baccetti* participated in the writing of the article related the "Reversed grading"; *Eugenia Gallo* participated in data analysis, contributed to updating the literature on use of botanicals and the writing of the article; *Fabio Firenzuoli* carried out clinical activities, conceived, designed, participated in the research, contributed to updating the literature on use of botanicals,and wrote the article.

Competing Interests

The authors declare no conflicts of interest.

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