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NATURAL PRODUCT–DRUG INTERACTIONS IN ONCOLOGY: CHEMICAL BASIS, PHARMACEUTICAL CONSIDERATIONS, AND CLINICAL IMPLICATIONS

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Abstract

Cancer patients frequently use natural products to help them with their illness in addition to their oncology treatment. Patients often choose to use complementary and alternative therapies to try to improve their overall quality of life and reduce adverse effects from their chemotherapy treatments. In many cases, patients are using herbal/multiple supplements or other phytochemicals at the same time as chemotherapeutic agents or targeted therapies. Unfortunately, this can lead to significant herb-drug interactions that can alter the patients' therapeutic outcome. These may occur via pharmacokinetic mechanisms (e.g., inhibition or induction of cytochrome P450 enzymes, transporters, or metabolism) and pharmacodynamic mechanisms (e.g., modifying the effectiveness or toxicity of the drug). The most common natural products that have been shown to have a potential effect on the absorption, distribution, metabolism, or elimination of chemotherapeutic agents and targeted therapies include St. John's Wort, turmeric, green tea, ginseng, garlic, and grapefruit. Knowledge of the chemical compounds responsible for these

interactions is necessary to promote optimal pharmaceutical care and limit the negative clinical consequences. This review will identify the chemical basis for natural product-drug interactions in the oncology population and note key pharmaceutical considerations of formulation and metabolism, as well as evaluate the clinical implications based on the current literature.

Keywords: Natural products; Herb–drug interactions; Oncology; Chemotherapy; Phytochemicals; Cytochrome P450; Drug transporters; Pharmacokinetics; Pharmacodynamics; Cancer therapy; Dietary supplements; Clinical implications

INTRODUCTION

Complementary therapy for cancer patients involves the use of alternative or natural product therapies to complement traditional medical therapies. Examples of these types of therapies include herbal remedies (for example, herbal teas), dietary supplements (i.e., vitamins), minerals, and other bioactive substances derived from plants. Patient use of natural products, such as herbal medicine and dietary supplements, to help manage treatment-related adverse events, enhance immune function, and alleviate symptoms of fatigue and nausea. Patient use of these products has grown in popularity due to their perceived safety as a result of being "natural." However, many products developed from nature contain pharmacologically active constituents that have the potential to alter the efficacy and/or safety of anticancer therapies due to the possibility of an interaction between the product and the anticancer agent being taken. Interactions between herbal and dietary supplement products and anticancer agents can alter the pharmacokinetics of the chemotherapeutic agents, thereby decreasing their therapeutic benefit or increasing their toxicity. The increasing popularity of complementary and alternative medicine has raised awareness about the importance of evaluating how natural products can be safely integrated into oncology practice. Studies suggest that many cancer patients are using herbal or dietary supplements without knowledge or notification of their healthcare provider, which could put them at increased risk for clinically significant interactions between the natural product(s) and anticancer therapies. Because of this, healthcare providers should routinely assess patients' use of natural products during medication evaluations and treatment plan development. Understanding the mechanisms of and clinical significance and consequences of these interactions is essential to ensuring that patients achieve optimal therapeutic outcomes, minimize adverse events, and receive evidence-based cancer care that is consistent with modern oncology standards of care. (Izzo & Ernst, 2009)

Natural products that interact with drugs in oncology are generally classified as having pharmacokinetic interactions via modulating drug metabolism and transport

mechanisms. The cytochrome P450 (CYP) system is involved in the metabolism of many chemotherapeutics, with some constituents from herbs ultimately leading to metabolic alterations of those drugs. St. John's wort (Hypericum perforatum), commonly known as a CYP3A4 and P-glycoprotein inducer, has been documented to decrease the plasma concentrations of imatinib, irinotecan, and docetaxel, resulting in significant reductions in therapeutic efficacy. Conversely, grapefruit juice has been reported to inhibit CYP3A4, leading to increased drug toxicity. In addition to modulating enzyme activity, natural products also have the potential to modulate drug transporters such as P-glycoprotein and organic anion-transporting polypeptide transporters (OATP), thereby affecting the bioavailability of the drugs. Given that many anticancer drugs have narrow therapeutic indices, even small changes in pharmacokinetics can lead to a large clinical effect. Thus, understanding the chemical constituents in herbal products, which may include flavonoids, alkaloids, and terpenoids that modulate CYPs and transporter activity, is vital for predicting and managing possible herb–drug interactions in cancer patients. (Posadzki et al., 2013)

In the field of cancer treatment, the influence of pharmacodynamic interactions between natural products and cancer chemotherapy should not be overlooked since they can have an effect on the final results of cancer treatment. As opposed to pharmacokinetics (the study of how drugs are absorbed, distributed, metabolized and eliminated from the body), pharmacodynamics refers to the direct and/or indirect effect of a substance (in this case, a natural product) on the biological activity (mechanism of action) of a chemotherapy agent without affecting its concentration. Numerous natural products derived from plants possess properties such as antioxidant, anti-inflammatory and immunomodulatory, all of which can disrupt or modify the intended mechanism of action of chemotherapy and/or radiation therapy. For example, green tea, vitamin E and curcumin all contain antioxidants that can help to lower oxidative damage; thereby, by reducing the number of reactive oxygen species produced in the body, decrease the effectiveness of certain cancer therapies that depend on the presence of these reactive oxygen species for cancer cell death. In contrast, some natural products may enhance the activity of anticancer therapies through synergism, thereby sensitizing cancer cells to undergo apoptosis. The complex and contextual nature of these pharmacodynamic interactions creates challenges when trying to determine effects upon treatment outcomes. On top of that, the variable nature of herbal products (eg. composition, dosing, and patient genetics) complicates the prediction of treatment response. Lastly, due to both the lack of standardized products and limited clinical studies examining the use of herbal compounds in cancer therapies, clinical decision-making is clouded

regarding the potential risks/benefits of using these products. Therefore, careful assessment of pharmacodynamic interactions is essential in oncology to help predict unanticipated conflicts with standard cancer treatments and to investigate any possible therapeutic benefit of using specific natural products. (Ruschitzka et al., 2000)

When looking at pharmacological issues surrounding natural product-drug interactions, there is difficulty in terms of formulation, dosing and therapeutic monitoring in oncology. The chemical composition of herbal products is variable due to their growing conditions, harvest methods and how they are processed; therefore, herbal products produce variable pharmacological responses. This makes it difficult to estimate the degree of risk for a natural product compared to an anti-cancer medication. In addition, natural products often contain several bio-active constituents that act on different molecular targets and create complexity to the potential interactions that will occur from the use of both products. Bioavailability, solubility and stability for both natural products and chemotherapeutics when administered together adds a level of complexity to the pharmacist managing these patients. Some constituents from herbal products change the pH level of the gastrointestinal tract or the activity of enzymes in the intestinal tract and impact the dissolution rate and absorption of prescription drugs. Other concerns for the pharmacist are that the use of advanced drug delivery systems such as nano-formulations to treat patients with cancer may have an unpredictable interaction with phytochemicals. There are additional concerns regarding the use of dietary supplements because they are not subject to very strict government regulations for quality control or clinical safety. Therefore, pharmacists have a very important role in evaluating potential herb-drug interaction risks, performing medication reconciliation, and making dosing adjustments when appropriate. Pharmacovigilance systems need to be developed to allow for the identification and management of adverse herb-drug interactions occurring in patients with cancer. (Zhou et al., 2004)

The clinical implications of natural product-drug interactions in oncology are considerable given their effects on patients' treatment and survival rates. Adverse interactions can be detrimental to the patient by causing drugs to be at subtherapeutic concentrations which allows tumors to continue to progress or leading to increased toxicity which may, in turn, lead to discontinuation of a treatment regimen. Most patients do not report use of herbal supplements because they believe these products are safe (harmless). Therefore, under-reporting of natural product-drug interaction cases is common. There are clinical studies that demonstrate natural product-drug interactions, occurring with commonly-used natural products, chemotherapy agents, targeted therapy agents, and immunotherapy agents. For example, ginseng and garlic

have been used as dietary supplements and studies have shown that the use of these two products can alter platelet aggregation and increase risk of bleeding in patients receiving myelosuppressive chemotherapy. Antioxidants may also reduce the effectiveness of radiotherapy by decreasing the amount of oxidative damage that occurs to cancer cells. To reduce the risk associated with natural product-drug interactions, it is important that healthcare providers adopt a multidisciplinary approach involving oncologists, pharmacists, and nurses when assessing patients. Routine screening for herbal use, educating patients about safe herbal use, and following evidence-based guidelines on herbal usage will also reduce the risk of interaction with chemotherapy treatment or other treatment modalities. Genetics should also be taken into consideration during clinical decision-making and have an impact on interactions. Genetic polymorphisms associated with drug metabolizing enzymes may affect how a patient may respond to a given treatment regimen that includes a chemotherapy agent and/or natural product. Integrating knowledge of natural product-drug interactions into clinical oncology will help improve the safety of treating patients with cancer. (Fasinu et al., 2019)

Natural product-drug interactions in oncology are still a developing and diverse area of research that crosses multiple disciplines. Natural products can provide support to patients with cancer; however, simultaneously using a natural product and an anticancer agent can present risks that are concerning. Advances in analytical chemistry have provided us with more information about the molecular mechanisms involved in these interactions, but concerns exist regarding the clinical evidence and standardized guidelines for these interactions. Future studies should focus on conducting clinical trials to support the safety, efficacy, and dose-response of commonly used herbal products by cancer patients. The creation of predictive models using pharmacogenomics and systems biology will help to predict interaction risk for individual patients. Regulatory efforts to ensure quality control and accurate labeling of dietary supplements also will contribute to patient safety. Education for both practitioners and patients is key to promoting the safe and effective use of natural products in the oncology setting. When risk is appropriately managed by ongoing monitoring and scientific validation, incorporating evidence-based complementary medicine into traditional cancer treatment will provide improved patient-centered care. (World Health Organization, 2020)

Natural products can interact with cancer drugs

Cancer patients frequently use natural remedies as an adjunct to conventional therapies. These include herbal medicine and other dietary supplements, as well as bioactive

compounds derived from plants, all of which have been positively viewed by the vast majority of patients as being safe and effective therapies. However, there is a possibility of clinically significant drug interactions between natural products and cancer medications. Such clinically meaningful drug interactions might occur due to differences in how drugs are absorbed, metabolized, distributed, or eliminated and therefore will affect the therapeutic effectiveness of the drugs used to treat cancer. Most patients who utilize herbal remedies (e.g., ginkgo, St. John's wort, echinacea, turmeric and so on) do not inform their health care provider of their use of these treatments, thereby increasing the risk of unintended drug interactions. Anticancer medications may have relatively small therapeutic windows, so changes in concentration (even small amounts) of the medications can result in serious toxicity or treatment failure. The potential for clinically meaningful drug interactions can be further complicated by differences in the composition of the herbal products used, the lack of standardization, and the limited clinical data available for herbal products. Overall, gaining a better understanding of how natural products and medications used to treat cancer interact and affect each other is fundamental to safe practice for oncology providers. Therefore, oncology providers should carefully assess their patients' use of complementary and alternative medicine and utilize their findings in developing treatment plans to minimize the risks of undesired drug interactions and maximize the effectiveness of the overall treatment process for cancer. (Yuan et al., 2016)

The pharmacokinetics of anticancer drugs can be modified significantly by natural products through their modulation of enzymes and drug transport systems. The cytochrome P450 (CYP) enzyme family, especially CYP3A4, CYP2C9 and CYP2D6, is involved in the metabolism of many drugs. For example, St. John's wort induces CYP3A4 and reduces plasma concentrations of some anticancer drugs (for example, irinotecan and paclitaxel), which may lead to therapeutic failure. By contrast, grapefruit juice inhibits CYP3A4, enhancing the bioavailability of drugs and thus the risk of drug toxicity. Natural products also interact with many drug transporters, such as P-glycoprotein (P-gp), which plays a role in regulating the efflux of drugs in the intestine and cancer cells. Studies suggest that ginseng and curcumin can act as modulators of P-gp activity and alter the distribution of chemotherapy agents. Changes in pharmacokinetics represent a serious concern in oncology, as anticancer agents require precise dosing to achieve maximum therapeutic benefit and to minimize toxicity. Additionally, genetic variation among patients can further complicate these interactions, leading to variable outcomes. Enhanced knowledge of the modulation of enzyme systems and transporters produced

by natural products will be critical for optimizing cancer pharmacotherapy and preventing adverse drug events. (Guengerich, 2017)

In addition to their effects on pharmacokinetics, natural products can also exert an influence on cancer medications via pharmacodynamics. At this level, the interaction of herbal ingredients with the biological activity of chemotherapeutic agents would be altered by modifications made to those same biological activities without affecting the overall concentration of the medications themselves. Many compounds derived from plants are known to have properties that can reduce damage caused by free radicals (i.e., antioxidants), limit inflammation (i.e., anti-inflammatories), and help modulate the immune response (i.e., immunomodulators). Although these different properties may be helpful to overall health and well-being, they can potentially interfere with the cancer therapy that relies on free radical-induced cell death to kill cancerous cells. For instance, antioxidants such as vitamin C, vitamin E, and polyphenols from green tea can decrease the effectiveness of radiation therapy and certain chemotherapeutics. However, natural products may enhance the anticancer properties of several chemotherapeutic agents by promoting apoptosis or preventing the growth of tumor cells (i.e., inhibiting proliferation). Curcumin, resveratrol, and berberine all appear to have synergistic properties with chemotherapy in laboratory studies. Due to the dual nature of herbal interactions, the precise clinical significance of these naturally derived agents remains difficult to discern. The absence of well-defined dosing parameters and variation in individuals' responses to similar actions adds further complication to the evaluation of pharmacodynamic interactions. Careful assessment of the potential pharmacodynamic interactions between herbal products and chemotherapeutic agents will be necessary to make certain that herbal products do not interfere with the effectiveness of cancer therapy. (Corsetto et al., 2017)

Herbal products that are considered cancer drugs and used along in oncology are affected by the different formulation, stability, and bioavailability properties of each product from their natural sources. Since there often are several active compounds in herbal products, it can be difficult to determine which specific active compound is the cause of the interaction. Each species of plant has variations due to the environment, time of harvest, or method of extracting the compounds. All of these aspects affect the chemical profile of that species and the impact these aspects have on the absorption of drugs or their metabolism when taken with an anticancer drug. There is also a possibility that some herbal products may affect the pH of the stomach or increase permeability to the intestine, therefore affecting the solubility of medications used during treatment for cancer. Several products can also bind to chemotherapy drugs; this would decrease the

bioavailability of chemotherapy drugs since those binding products will not be absorbed into the body. Because the products that dietary supplements are considered to be very loosely regulated, there is a greater chance of contamination and inaccuracy on product labels. Pharmaceutical scientists also have difficulty predicting what the possible interactions could be because of a lack of clinical trial data and no standardized way to develop and evaluate the products. Some researchers investigate unfolding delivery systems, such as nanoparticles and liposomal formulations, and their possible interactions with the phytochemicals in some herbal products. Therefore, the pharmacist is important in evaluating for potential interactions and in monitoring quality control of herbal-based products and in providing the appropriate education to individuals using complementary therapy for the treatment of cancer. (Liu et al., 2019)

(Natural product-drug interactions) can have serious negative impacts on treatment for patients with cancer. These (interactions) can result in decreased efficacy, increased toxicity, and an unexpected adverse event. Many patients do not take the opportunity to inform their healthcare providers of their herbal supplement use; therefore, providers are uninformed of any potential risks they may pose to them. For example, both garlic and ginkgo can cause an increased risk of bleeding for those receiving chemotherapy that affects the ability of their platelets to function. Antioxidants can decrease the efficacy of both chemotherapeutic and radiotherapeutic medications. Furthermore, the outcome of treatments involving the use of immunotherapies can be altered by using immune-modulating herbs. These examples demonstrate why providers should conduct a routine screening for amateur use of herbs (during) patient assessments. Collectively, oncologists, pharmacists, and nurses working together will provide patients with effective management of these interactions. It is equally important to educate patients about the potential risks of using any herbal products without the supervision of a qualified healthcare professional. Guidelines should be developed to ensure that clinical decisions in integrative oncology are evidence-based. Personalized treatment plans that are based on patient genetics and prior medical history will additionally reduce the potential for drug/herb interactions and improve patient outcomes. (Wang et al., 2020)

Interactions between cancer therapeutics and natural products can be complex and result from several different mechanisms. Pharmacokinetics, or how drugs are processed in the body, as well as how the drug affects the body, are examples of both types of mechanism. Natural products are commonly used to support patients undergoing cancer treatment. Nevertheless, the potential for altering the effectiveness of these medications via altered drug metabolism (via pharmacokinetics) or differing

therapeutic response (via pharmacodynamics) must be considered in making recommendations for patient care. The overall complexity of the potential interactions between cancer therapeutics and natural products is made more unlikely due to natural products variable composition, lack of standardization and an overall lack of sufficient clinical evidence. The role of pharmacists and other healthcare professionals is to monitor and educate patients regarding the potential interactions between natural products and cancer therapeutics as well as how to manage these interactions. Future research should include large-scale, controlled clinical studies in order to establish the safety and efficacy of natural products that are commonly used by cancer patients. Additionally, increased regulatory oversight and the establishment of good manufacturing practices are needed to produce standard products. Any use of complementary (nature-based) medicine must be done only after determining whether the risks associated with their use are manageable. To ensure the provision of safe cancer treatment, there must be a balance between the effectiveness of the prescribed treatment(as demonstrated through the scientific process) versus the cautious and judicious use of nature-based products in order to prevent harmful interactions from occurring. (Pal & Mitra, 2021)

Interactions may reduce efficacy or increase toxicity

The presence of natural products can greatly affect cancer drugs through the way they interact with an anticancer drug's metabolism or response. Interactions are particularly significant in cancer because of the narrow therapeutic index associated with many chemotherapy agents—the likelihood that minor variances in drug levels can have considerable clinical consequences. Many patients will take herbal remedies and dietary supplements in conjunction with chemotherapy without consulting with their physician or other healthcare providers. Biological active components contained in natural products can influence drug pharmacokinetics and pharmacodynamic behavior. Consequently, anticancer drugs may have levels that are either sub-therapeutic for controlling tumor growth, or supra-therapeutic resulting in excessive adverse events (e.g., the drug-masking effects of enzymatically induced herbs leading to faster therapeutic drug metabolism, whereas the drug-masking effects of enzymatically inhibiting substances will yield greater than anticipated toxicity). Additionally, while there are many mechanisms by which herbal products can influence how a drug will influence pharmacokinetics and pharmacodynamics, some products can likely influence the distribution of the drug within the body through use of drug transporters. There is, therefore, a need for a thorough evaluation of the use of complementary forms of treatment in cancer patients. Knowing reasons why a patient may have lower than

expected efficacy and/or higher than expected toxicity associated with drug therapy will assist in improving safety of treatment and outcomes associated with the management of cancer patients in the future. (Bensoussan et al., 2017)

Natural product-drug interactions can have major consequences. One such consequence is the decreased efficacy of anticancer therapy. This may result from the increased metabolism and/or elimination of chemotherapy agents as a result of herbal compounds that give rise to sub-therapeutic levels of drug exposure. As an example, St. John's Wort promotes activity of certain cytochrome P450 enzymes, such as CYP3A4, and thereby increases the metabolic breakdown of therapeutic agents, including irinotecan and imatinib, which can lead to decreased plasma concentration of the drug and tumor progression or failure of treatment. Many herbal supplements also stimulate activity of P-glycoprotein, thus facilitating the efflux of drug out of cancer cells and lowering the amount of drug available to kill cancer cells; thus the intended cytotoxic effect on the tumor will be compromised. Reduced efficacy due to these factors is particularly troublesome in patients with aggressively growing cancers, where timely and adequate drug action is an important determining factor in patient outcome. Patients often lack knowledge that their use of herbal supplements is negatively impacting their treatment, which results in continuing to use these products, even when they are not achieving good clinical response. These examples demonstrate the importance of monitoring the intake of herbal products, and adjusting the doses of chemotherapy as needed. Clinicians must be knowledgeable about the presence of enzyme-inducing natural products to avoid loss of therapeutic benefit when treating patients with cancer. (Izzo et al., 2016)

Natural products may also enhance anticancer drug toxicity through inhibition of drug metabolism and/or clearance. Herbal products that inhibit cytochrome P450 enzymes or drug transporters can lead to the accumulation of chemotherapy in the bloodstream at high enough levels to cause adverse effects. Grapefruit juice is an example of an inhibitor of CYP3A4. Its use can greatly increase plasma concentration of many anticancer drugs and contribute to adverse events such as hepatotoxicity, nephrotoxicity, and myelosuppression. In addition, some herbal antioxidants and flavonoids affect drug detoxification enzyme pathways. Increased toxicity from these interactions may result in dose-limiting toxicity that delays or decreases therapy, which can negatively impact long-term control of cancer and ultimately affect patient survival. These potentially toxic drug interactions are of particular concern in the elderly and in patients with liver or kidney dysfunction. Patients often do not disclose to their healthcare providers that they use natural products as they are viewed as non-

threatening; therefore, the potential for toxicity is likely underestimated. Accordingly, health care providers should routinely assess for the use of herbal products during the development and monitoring of an oncology treatment plan. Inhibitory interactions should be well understood to avoid potentially life-threatening adverse effects in patients receiving oncology treatment. (Zhang et al., 2018)

Many anticancer drugs are metabolized mainly by using cytochrome P450 (CYP450) enzymes, and the induction/inhibition by natural products of CYP450's will play an important role in determining how drugs will interact. P-glycoprotein (Pgp) and other efflux transporters will control how much of a drug may get into a cell or tissue. Herbal compounds such as flavonoids, alkaloids, and terpenoids can either stimulate or inhibit drug-metabolizing enzymes or drug transporters. There are both stimulatory and inhibitory effects of different natural products on drug activity and toxicity. Absorption from the gastro-intestinal tract, protein binding, and renal excretion are also affected by the use of herbal products and will determine the variability of drug response. Further, genetic differences in patients will affect these interactions and result in unpredictable drug responses. In addition, the combined actions of many active components in a herbal mixture will contribute to further complexity as each component may have effects on multiple targets at the same time. Therefore, understanding the molecular mechanisms will be necessary for predicting clinical outcomes and developing safer treatment strategies for cancer. (Gurley et al., 2019)

Cancer patients face serious risks from natural products containing potential for reduced drug effectiveness and/or increased toxicity. Reduced drug effectiveness may lead to greater disease progression, more metastases and/or recurrence, while the increased toxicity from natural products often leads to hospitalization and/or discontinuation of cancer therapies. All of these result in a major impact on patient survival and on patient quality of life. Patients often do not report use of herbal supplements which makes it difficult for clinicians to identify the cause of unexpected treatment responses. Failure for patients to inform healthcare providers about use of herbal supplements is one of the main barriers to safe management of cancer patient care. The variability in the composition of herbal products also creates difficulties in developing standardized clinical predictions. A proactive approach using routine medication history review, patient counseling, and pharmacovigilance systems will allow healthcare teams to identify potential risks and hazards at an early stage. Multidisciplinary cooperation is also necessary to effectively manage these interactions. Additionally, clinical education and awareness will have an important effect on reducing

the occurrence of adverse events that are associated with the use of natural products in oncology. (Li et al., 2017)

In summary, the presence of natural product–drug interactions in the cancer care setting may lead to diminished effectiveness of anticancer agents and/or increased toxicity of anticancer therapies, thus creating significant risks to patients. These interactions occur via complex pharmacokinetic and pharmacodynamic processes related to the metabolism and transport of drugs, as well as cellular signaling pathways involved in the action of drugs at the level of the target site. Although natural products have become increasingly widely utilized as adjuncts to treatment, their potential for interaction should not be trivialized by health care professionals considering treatment options for patients with cancer receiving high-risk therapy. The use of natural products can also increase the potential for adverse events due to a lack of standardization, limited clinical experience, and limited patient reporting of natural product use to their health care provider. Therefore, health care providers must perform a thorough evaluation of a patient's use of herbal products and/or dietary supplements prior to any treatment for cancer in order to promote safe and effective cancer care. In order to minimize the risk associated with using complementary therapies, it will be necessary to increase awareness, educate patients, and create evidence-based guidelines for the use of complementary medicines. Future research should include studies identifying herbal products that carry a high potential for adverse interactions and developing predictive models to assess the potential for interaction. The incorporation of this information into clinical oncology will enhance patient safety, improve cancer patient survival, and allow for the informed use of complementary medicines when needed. (Wanwimolruk et al., 2014)

Drug metabolism and transport are commonly affected

The primary mechanisms of action for the influence of natural products on how anticancer drugs work pharmacokinetically, or the way drugs move through the body, are drug metabolism and transport. This is especially important in oncology where the precise dosing of chemotherapy agents is necessary in order achieve the best therapeutic effect, without producing life-threatening toxicity. Naturally occurring substances, including herbal medicines, dietary supplements, and phytochemicals, can alter the activity of metabolic enzymes and transport proteins, significantly changing how much drug is available to the patient. Of particular importance in the metabolism of drugs is the cytochrome P450 system of enzymes, especially CYP3A4, CYP2C9, and CYP2D6 which are responsible for the biotransformation of a large number of drugs. There are also transporters (P-glycoprotein) that regulate the movement of drugs across

the cell membrane by transporting drugs out of the cell. When natural products interact with either of these systems, they can cause an increase or decrease in drug clearance or elimination. As a result, a patient may either have too low a concentration of the drug (subtherapeutic) or too high a concentration of the drug (toxic). The use of multiple medications combined with the addition of complementary therapies by patients with cancer increases the probability that a drug-drug interaction will occur. Therefore, an understanding of the effects of natural products on the processes of metabolism and transport is critical in providing for safe and effective administration of chemotherapeutic agents. (Brantley et al., 2018)

One of the key ways that drugs interact is by modulating cytochrome P450 enzymes. Many natural substances contain compounds that may either enhance or suppress drug metabolizing CYP enzymes. For instance, St. John's Wort is a potent inducer of CYP3A4 and can enhance the metabolism of some anticancer drugs (ex: docetaxel, irinotecan), resulting in lower plasma concentrations and reduced efficacy for these drugs. Conversely, grapefruit juice inhibits CYP3A4, which may lead to higher drug concentration and increase the risk of toxicity from these drugs. Other herbal products (ex: ginseng, echinacea) may also conflictingly modulate CYP activity depending on the concentration and method of preparation. The importance of these interactions is amplified in the setting of cancer treatment as small differences in drug doses can greatly influence the outcome of the therapy. The inherent differences in the expression of enzymes in individual patients make it difficult to predict the degree to which a patient will experience an interaction. Chronic use of herbal products may affect long-term enzyme function and alter steady-state concentrations of the drugs that are metabolized by CYP enzymes. Due to the critical nature of these interactions, it is crucial to closely monitor the use of herbal products and their potential effects on drug metabolism when treating cancer. (Fasinu et al., 2018)

Numerous natural products have been documented to influence transporter function, including the class of molecules known as drug transporters, which includes proteins such as P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptides (OATPs). These transport proteins are responsible for the absorption, distribution, and elimination of many anticancer agents. The many herbal-derived compounds reported to have an impact on P-gp activity include curcumin, resveratrol, and quercetin, with some of these agents stimulating drug transport from the cell via P-glycoprotein (P-gp) whereas others inhibit this efflux of drug from the cell. Induction of P-gp leads to enhanced efflux of anticancer agents from cancer cells and results in diminished intracellular concentrations of drug which then

diminishes the pharmacological efficacy of the drug at the site of action. Conversely, inhibition of P-gp leads to increased accumulation of drug in cancer cells and could potentially lead to toxicity. Both of these scenarios play an important role in the treatment of multidrug resistant cancers in which overexpression of these transporters already diminishes the effectiveness of therapeutic agents due to excessive efflux of drug out of the cancer cells via P-gp. Effects of natural products on transporter function may have a considerable impact on chemotherapy resistance and responsive. The combined effects of modulation of the enzyme and transporter function makes predicting the behavior of drugs exceedingly complex. Understanding these transporter interactions is necessary for enhancing drug delivery and overcoming resistance in cancer treatment. (Shen et al., 2019)

Natural products can very much change the bioavailability of anticancer drugs through effects on both metabolism and transport processes. Bioavailability is usually defined as the portion of drug that reaches systemic circulation in active form after administration. If an herbal product speeds up metabolism or increases efflux transporter activity, the amount of drug that is bioavailable will decrease and thus provide a lower therapeutic effect. Conversely, when an herbal product inhibits the activity of metabolic enzymes or transporters, the bioavailability will increase to dangerous levels, resulting in potential toxicity. For example, flavonoids found in citrus fruits and green tea may manipulate the intestinal absorption of specific chemotherapy agents. Many herbal compounds also have the ability to bind directly to drugs in the gastrointestinal tract thereby limiting their absorption. The interactions between herbs and drugs depend on dose, time of administration, and patient-specific factors. Cancer treatment requires precise exposure to the drug, which means that even small changes in bioavailability can lead to meaningful clinical differences. Therefore, understanding how natural products affect both metabolic pathways and transport pathways is necessary for the optimal use of cancer pharmacotherapy. (Kumar et al., 2017)

In oncology, the clinical significance of alters in the metabolism and transport of drugs is great. When there are alterations in drug metabolism or transport, the result may be unexpected and can result in reduced tumor response or increased adverse effects. Many patients combine the use of herbal supplements with chemotherapy without being aware that it could produce unintended clinically significant interactions. For example, if a patient had a decreased metabolism of a drug, then this could produce pathological levels of toxicity (e.g., depression of bone marrow function) or if they had an increased metabolism of the drug, then they may not respond to treatment or achieve the desired outcome. The alteration in the function of transporters may also be

a contributing factor to the development of multidrug resistance, a common impediment to cancer treatment. Healthcare providers have difficulty identifying such interactions because patients frequently do not disclose the use of herbal supplements and/or the variability of the constituents in an herbal preparation. Therefore, routine assessment for the use of dietary supplements must be performed as a component of the normal process of care that a patient receives in an oncology practice. The role of pharmacists is critical for this process in that they can help the healthcare professional identify potential risks and provide recommendations about changes that may be necessary. In addition, patient education is a significant component of informing patients about the potential of contributing to their treatment being non-effective due to herb-drug interactions. A multidisciplinary approach will be necessary to effectively manage these complex interactions and maximize the level of safety of the patient's treatment. (Wang et al., 2018)

In summary, natural products commonly affect drug metabolism and transport, making them one of the major sources of herb-drug interactions in cancer treatment. The interactions typically involve the modulation of cytochrome P450 enzymes and drug transporters, such as P-glycoprotein. These changes in drug bioavailability can lead to decreased efficacy or increased toxicity of anticancer drugs. The anticancer drugs are often prescribed at their narrowest therapeutic windows, and therefore even a small change in pharmacokinetics can have significant clinical implications. The complexity of these interactions is compounded by variability in the composition of herbs, patient genetics, and the lack of standardization. Physicians must closely monitor the use of herbal products and take potential interactions into consideration when planning treatment to provide cancer patients with safe and effective treatment. Increased education, better regulation of herbal products, and more clinical research will help to understand the mechanisms of action. The successful integration of pharmacokinetic knowledge into cancer treatment will improve treatment outcomes and patient safety while allowing for the cautious use of complementary medicine if appropriate. (Guengerich, 2017)

Clinical monitoring is essential

Monitoring patients in an oncological setting is critical to ensure patient safety and prevent potential side effects due to drug interactions as a result of the use of multiple drugs or products (including complementary and alternative treatments). All chemotherapy (anticancer) drugs have narrow therapeutic indices; thereby, dosages need to be adjusted according to how well the drug works for the individual patient (i.e., therapeutic drug monitoring). There are numerous examples of how

complementary/alternative therapy can impact how a drug is absorbed/metabolized/excreted; therefore, continuous monitoring of the patient must occur. If proper monitoring does not occur, patients may present with serious organ damage, absent tumor response, or adverse reactions that progress to high levels of severity (adverse effects) before being recognized when compared to tolerable levels of experience/presenting with the drug. Clinical monitoring includes evaluation of patient history; performing laboratory tests; performing therapeutic drug monitoring; monitoring response to treatment; and asking about the patient using, or has ever used, any complementary or alternative therapies at every clinical check-up. Therefore, systematic and organized clinical monitoring is an integral part of providing safe and effective supportive oncologic care, so that chemotherapy (conventional) and natural treatments are utilized safely and appropriately together. (Efferth et al., 2017)

A detailed review of the patient's medication history is critical to the clinical treatment of patients with cancer. Some patients may not volunteer to disclose the use of any complementary therapies; some do not consider these product types to be evidence based, and therefore do not think they will have a negative impact on their health. It is necessary for physicians to ask direct and non-judgmental questions about the patient's use of all types of medications in order to obtain a complete medication history. A complete medication history should include prescriptions, over-the-counter medications, vitamins, and herbal products. Once all medications are documented, clinicians can evaluate the potential for drug interactions with chemotherapy agents. For example, both St. John's wort and ginseng (as herbal products) have been associated with an increase in the metabolism of other drugs and a higher risk of bleeding when co-administered with other drugs used in cancer treatment. If clinicians do not ask about the patient's history of complementary therapy use, these interactions may remain hidden. Because pharmacists are key to reviewing a patient's medication profile, they can assist clinicians in identifying potential risks associated with these types of products. In addition, medication records need to be up-to-date because patients may begin or discontinue using complementary therapies during their cancer treatment. Therefore, having a structured process for reviewing medication histories is important to prevent harmful drug interactions and promote safe cancer treatment. (Dawood et al., 2018)

Clinical supervision for patients with cancer using natural products consists of many components, one of which is laboratory testing and diagnostics. Some examples of laboratory tests for oncology patients using natural products include blood tests, liver function tests, renal function tests, and complete blood counts, all of which can assist in

the early detection of evidence of possible drug toxicity or altered drug metabolism. For instance, elevated liver enzymes may be indicative of how some herbal products can inhibit the metabolism of other drugs, while abnormal renal function may indicate that some herbal products affect the elimination of that same drug from the body. Therapeutic drug monitoring (TDM) may also be performed in patients on specific antineoplastic therapies to assist in ensuring that the drug concentration of that therapy remains within the therapeutic range. Imaging studies and tumor markers can also be used as part of clinical supervision to assess the efficacy of treatments and if there is a potential decrease in efficacy with the use of natural products. Many natural products may have an indirect effect on the above parameters through altering the pharmacokinetics of that drug and/or the body's immune response to the drug. By regularly performing laboratory assessments on oncology patients who are taking herbal products, the clinician will have a more effective means to modify the dose of drug, if necessary, in a timely manner to prevent complications. Additionally, regular laboratory assessments may assist in differentiating between normal disease progression and the effects related to drug interactions. The majority of herbal products are not associated with predictable outcomes, which emphasizes the need for routine laboratory assessments to identify drug toxicity or ineffective treatment at the earliest possible time. Therefore, the use of diagnostic laboratory tests in oncology patients using natural products provides objective data on how to provide safe and effective treatments for cancers through the use of pharmaceuticals. (Izzo et al., 2016)

In treating patients using both anticancer therapies and natural substances, monitoring for adverse effects is very important. Adverse reactions occur through pharmacokinetic or pharmacodynamic interactions producing either increased toxicity or decreased efficacy of these drugs. Hepatotoxicity, nephrotoxicity, myelosuppression, and gastrointestinal disturbances are common toxicities observed. Herbal supplements could enhance the toxicity of build-up of the anticancer agents by decreasing their renal clearance as examples of how an antioxidant supplement could potentially interrupt the oxidative stress mechanism of chemotherapies, while some herbal substances may increase bleeding tendencies and give rise to immunosuppressive effects. Examples of toxic signs to continuously assess for early detection of adverse effects include fatigue, nausea, bruising, and infection. Patient self-reports and clinical-based toxicity scales can be used to systematically measure the level of toxicity. Timely intervention can then be made by altering the dose or discontinuing the herb(s). Poorly monitored symptoms may lead to an increase from mild to extreme and/or life-threatening adverse reactions. Employing structured methods of monitoring adverse reactions is therefore critical for

ensuring the safety of care and for improving the quality of life in all patients receiving oncology treatment. (Posadzki et al., 2013)

Effective clinical monitoring of oncology patients who use natural products involves a multidisciplinary approach. This approach utilizes a team made up of oncologists, pharmacists, nurses, and other members of the healthcare team to provide comprehensive management of the oncology patient. Each member of the healthcare team brings different expertise to the table when it comes to identifying, preventing, and managing drug interactions. Pharmacists are the medication reconciliation experts and the experts in screening for possible drug interactions; oncologists are the ones who make the treatment plans and adjustments to medications; and nurses frequently are the ones who monitor patients for symptoms and ensure compliance with their therapy. Communication between all members of the oncology team is critical in order for all members to identify the risk associated with using herbal products. The members of the multidisciplinary team will also be responsible for educating cancer patients about the risks associated with the use of natural products in combination with chemotherapy. The use of regular team meetings and shared electronic medical records by the members of the multidisciplinary team will assist in the coordination of care and reduce the likelihood that drug/drug interactions are missed. Through the use of a multidisciplinary approach, patient safety will be improved, treatment outcomes will improve, and the cost of healthcare associated with adverse drug reactions will decrease. Therefore, the use of a multidisciplinary care approach is essential for effective clinical monitoring of patients in today's oncology practice. (Wang et al., 2019)

In summary, clinical monitoring is critical for the safe management of drug interactions caused by natural products in oncology. Continuous evaluation of patient history, lab values, adverse effects, and treatment response aids in detecting potential risks before they become serious complications. Because anticancer medications possess small therapeutic windows, even small interactions with herbs have the potential to greatly impact treatment outcomes. Comprehensive monitoring confirms efficacy and safety throughout treatment. The participation of interdisciplinary healthcare teams provides greater likelihood of identifying and managing interactions. Further, patient education is key to enhancing the disclosure of herbal medicine use to encourage safe practices. The future healthcare system must establish structured monitoring procedures and create pharmacovigilance systems to allow healthcare professionals increased ability to manage herb-drug interactions. Educating both healthcare practitioners and patients about the dangers associated with unsupervised use of natural products will decrease the likelihood of adverse events occurring.

Therefore, effective clinical monitoring enables evidence-based, patient-centred oncology care and will enhance therapeutic effectiveness. (Gurley et al., 2019)

Patient counseling improves treatment safety

Counseling cancer patients about their use of natural products is crucial in enhancing the safety of the oncology treatment. This type of counseling allows the patient to understand how the use of herbal and dietary supplements along with prescribed anticancer medications could have potentially serious effects on the way their medications will be processed and how effective those medications will be, as well as the risk they may carry for the patient.Despite the belief that natural products are safe, cancer patients alone may be using a combination of natural products that will alter some aspect of the processing of their prescribed medications. With proper counseling by healthcare practitioners, patients will be able to understand the potential for herb-drug interactions and be encouraged to report all forms of complementary medical care that they receive, regardless of the source (e.g. herbal or over-the-counter products) or their location (e.g. home, store, online).This type of communication is critical for patients because not reporting their use of herbal products can cause unexpected reaction to treatment that may result in failure to treat, increasing the likelihood of kidney damage or causing unexpected side effects from treatment, and affect the patient's outcome of treatment. In addition, counseling allows for patients to understand how natural products cannot be used as an alternative to their prescribed chemotherapy treatments.Counseling should occur at all levels of patient care and be individualized to each patient's needs and consideration given to their cultural beliefs and health literacy. Counseling by all members of the patient's healthcare team will allow for a more comprehensive approach to counseling the patient.Ultimately, counseling patients on their use of natural products will lead to safer use of medications, improved clinical outcomes, and decreased incidence of preventable complications when patients use complementary medicine. (Kennedy et al., 2018)

One of the main purposes of counseling patients is to increase their awareness of how natural products and drugs can interact adversely. Many patients think of herbal products as being safe due to their natural origin and use them without oversight or regulation. Through education, counseling helps address this misunderstanding by providing sufficient clear evidence about potential interactions of herbal products with chemotherapy medications. An example of this would be educating the patient about St. John's Wort and how it can decrease effectiveness of a chemotherapy drug or grapefruit products potentially increasing its toxicity. Increasing the awareness of the patient to report all supplement use to their healthcare professional will help improve healthcare

professionals' ability to plan for treatment. Providing appropriate education regarding timing, dosage and consistency of medications will also help patients to better utilize their medications. To enhance education, the use of visual aids, brochures and verbal explanation may also increase understanding. Counseling that is culturally sensitive can provide all patients of all backgrounds with sufficient and appropriate education. By providing better awareness of the issues discussed above, patients will be able to make better decisions regarding the use of medication and less likely to engage in unsafe self-medication practices. Therefore, the provision of patient education for counseling purposes is a critical intervention to reduce adverse events and improve the safety of patients being treated in Oncology. (Smith et al., 2017)

Counseling for patients significantly affects their adherence to treatment regimens when undergoing cancer therapy, because it provides education about any fears or misconceptions they may have concerning their current chemotherapy regimen. Patients often discontinue chemotherapy or change the dose because they experience too many side effects or because they have heard about alternative therapies for cancer treatment. Counseling assists patients to understand the value of completing the prescribed course of therapy in order to achieve the highest level of control over their cancer. Patients are also given a clearer understanding of the risks associated with using natural products in place of evidence-based therapies for the treatment of cancer. Healthcare providers will help patients to manage the side effects of their anti-cancer medications; this will decrease the likelihood that patients will turn to unproven herbal remedies to treat their side effects. Furthermore, during counseling, patients will receive information about taking their medication at the correct time and at the correct dose. In addition, as patients learn about how anti-cancer medications work, they are also more likely to comply with their prescribed treatment plans. Open lines of communication between patients and their healthcare provider develop trust, which in turn will contribute to a greater level of compliance. In addition to the points made above, when pharmacists dispense medications pharmacists help reinforce the counseling message to the patient (Horne et al., 2019)

Counseling patients is an important step in decreasing the risk of herb-drug interactions in patients receiving oncology treatment. Most patients do not realize that the use of herbs or herbal supplements may negatively impact chemotherapy agents due to their potential for interaction via various complex pharmacokinetic and pharmacodynamic pathways. By providing this type of targeted education to patients about high-risk herbal products and their possible effects on drug metabolism and toxicity, the patient is directed to refrain from using self-medicated agents and to

consult with a qualified health care professional before starting any new product. Counseling also emphasizes that patients should inform their physician about every type of herb or dietary supplement they are using so that the physician can make any necessary modifications to their treatment plan and prevent possible herb-drug interactions from occurring. Another aspect of suggested counseling is that patients need to understand appropriate timing when taking medication versus using herbal or dietary products, which can decrease the risk of drug interactions. For example, separating the use of an herbal product from chemotherapy administration may reduce the likelihood of absorption-related interactions. Ongoing counseling throughout the course of treatment will help ensure that the patient has the most up-to-date information regarding treatment as it continues to evolve. The timely provision of this proactive information will significantly lower the rates of developing an adverse drug reaction and help ensure patient safety. Thus, patient counseling can be considered a vital component of a preventive strategy in helping to effectively manage herb-drug interactions in clinical oncology practice. (Nieuwlaat et al., 2017)

Oncologists, pharmacists and nurses are directly involved in the provision of both effective patient counselling services. They each play a distinctive role in promoting safe treatment through their interactions with patients. Oncologists counsel patients about their cancer treatment regimens and what to expect from each regimen, while pharmacists primarily counsel about the safety and potential drug interactions of prescribed medications. Nursing staff tend to have the highest level of contact with patients and can often reinforce the messages they receive through the course of ordinary patient care. Successful counselling requires the use of clear messages, empathy and a patient-centred approach to provide the best possible outcome for the patient. All members of the health care team should consider a patient's language/culture and health literacy when providing them with information about their treatment. Research indicates that the provision of training in communication skills to health care professionals leads to more productive counselling sessions. By collaborating as a team, all members of the health care team can ensure that patients are receiving a consistent message and, thereby, reducing patient confusion. The documentation of all patient counselling conversations is critical to continuity of care. By working collaboratively, health care teams can ensure that patients are fully educated about the risks associated with natural products. This collaborative approach results in improved treatment safety and a reduction in preventable complications associated with oncology care. (Brown et al., 2018)

As stated above, the importance of patient counseling to achieve safe and effective cancer care in the management of medications used with natural herbal/dietary supplements cannot be overstated. The benefits of patient-Safe, effective patient education can increase the patient's understanding of their therapies, improve compliance with drug therapy, and limit the potential for patient-simultaneous use of various medications/dietary/herbal supplements leading to adverse side effects. The establishment of open lines of communication occur between patients and their healthcare providers is vital in order to facilitate effective treatment planning and ongoing monitoring of their treatment outcomes. Patient counseling serves as a valuable tool to assist in identifying and preventing potential risks associated with the unreported/misreported use of natural supplements/herbs on the part of many cancer patients. A collaborative, multidisciplinary approach to patient counseling will enhance the ability of the individual patient to receive a unified counseling perspective across various healthcare settings. Consistent educational and support reinforcement throughout the duration of treatment will help ensure the continued safety of the patient. In developing future strategies related to healthcare, oncology departments should prioritize the development and implementation of structured patient counseling programs and patient education initiatives. Increasing the effectiveness of the patient/provider communication process should ultimately contribute to better patient treatment outcomes, decreased levels of toxicity, and improved overall quality of life for cancer patients. For these reasons, patient counseling remains a fundamental component of providing safe and effective, integrative cancer therapies. (Ekor et al., 2018)

Conclusion

Interactions between natural products and drugs in oncology create a complex and challenging clinical dilemma that has the potential to profoundly alter clinical outcomes and the safety of treatment. While many cancer patients use natural products such as dietary supplements and herbal products for the purpose of supportive care, these agents are not without pharmacological activity. That is, many of these products may alter the pharmacokinetics and pharmacodynamics of anticancer drugs, by altering their metabolism (by affecting drug-metabolizing enzymes), their transport (by affecting drug transporter proteins), and cellular signalling (e.g., by affecting cell surface receptors or the pathways that mediate a cellular response). Therefore, interactions will occur between complimentary medicines and anticancer drugs that cause either an unacceptable reduction in the efficacy, or an unacceptable increase in the toxicity of one or both medications, or an unpredictable treatment response to one or both

medications. The problem of recognising these types of interactions is compounded by the large amount of variability present in the composition of herbal products, the lack of industrial or regulatory standardisation or assurance of product quality or clinical efficacy; and the limited clinical evidence about the effectiveness of the respective products. There is also a considerable concern that patients are often unwilling to disclose use of complementary medications, thereby creating unrecognized interactions of considerable potential clinical ramifications during the delivery of care. To mitigate these interactions, an integrated, team-based approach involving an oncologist, pharmacist, and nurse, along with a proactive approach to reviewing medications and educating patients continuously during therapy would be beneficial. Both clinical monitoring and patient counselling will also be required to ultimately mitigate risk and provide safe therapy. Future studies need to focus on the development of high-quality clinical evidence to support use of standardised guidelines for the safe integration of natural products into the care of persons with cancer.

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