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Herbal Medicines as Adjuvants for Cancer Therapeutics

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Abstract

In the United States, many patients, including cancer patients, concurrently take prescription drugs and herbal supplements. Co-administration of prescription medicines and herbal supplements may have negative outcomes via pharmacodynamic and pharmacokinetic herb-drug interactions. However, multiple constituents in botanicals may also yield beneficial pharmacological activities. Botanicals could possess effective anticancer compounds that may be used as adjuvants to existing chemotherapy to improve efficacy and/or reduce drug-induced toxicity. Herbal medicines, such as ginseng, potentiated the effects of chemotherapeutic agents via synergistic activities, supported by cell cycle evaluations, apoptotic observations, and computer-based docking analysis. Since botanicals are nearly always administered orally, the role of intestinal microbiota in metabolizing ginseng constituents is presented. Controlled clinical studies are warranted to verify the clinical utility of the botanicals in cancer chemoprevention.

Keywords

Botanicals; Herb-Drug Interaction; Colorectal Cancer; 5-FU; Irinotecan; Ginseng; Valerian; Astragalus; Turmeric; Intestinal Microbiota; Metabolites; Ginsenosides; Panaxadiol; Compound K

Introduction

In traditional medicinal systems, herbal medicines have been used to treat different medical conditions, including symptoms associated with cancer (Xu *et al.*, 2011; Zeng *et al.*, 2011). Several national surveys indicate that at least one third of American adults take some form of dietary supplement, and botanicals comprise approximately 25% of the supplement market (Barnes *et al.*, 2004). There is increasing evidence that in the U.S. cancer patients likely take botanical supplements concurrently with their chemotherapeutic agents (Ernst, 2000; Ma *et al.*, 2011). However, co-administration of botanicals and prescription medications may have negative outcomes due to herb-drug interactions (Aung *et al.*, 2007; Yang *et al.*, 2010).

Herbal medicines contain many different constituents, and they have variable pharmacological activities (Liao *et al.*, 2010; Wang *et al.*, 2011b). Botanicals could possess effective anticancer compounds that may be used alone or as adjuvants to existing

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chemotherapy regimens to improve efficacy and/or reduce drug-induced toxicity (Ott, 2002; Tian *et al.*, 2010).

In this article, we will first briefly discuss herb-drug interactions that may affect drug therapies. Then, emphasis will be placed on whether herbal medicines, such as ginseng, could enhance the effects of chemotherapeutic agents. Potential underlying mechanisms of actions of the synergistic effects observed in *in vitro* models will be presented. Since botanicals are virtually always administered orally, the role of intestinal microbiota in metabolizing herbal constituents will be discussed.

Mechanisms of Herb-Drug Interactions

Because ginseng is a very commonly used herbal medicine in the U.S., this botanical will be used as an example to illustrate the constituent complexity of herbal medicines. Ginseng consists of over 100 ginsenosides, in addition to many peptides and polysaccharides (Qi *et al.*, 2011b). Ginseng has a number of reported pharmacological activities in both animal and human studies (Jang and Shin, 2010; Jung *et al.*, 2011), and its multiple constituents are responsible for these observed effects (Attele *et al.*, 1999; Qi *et al.*, 2011a). This constituent diversification of ginseng can be applied to most herbal medicines (Al-Suhaimi *et al.*, 2011). Concurrent administration of herbal medicines and prescription drugs can initiate complex pharmacodynamic and pharmacokinetic changes in administered drugs (Wang *et al.*, 2010). Understanding the herb-drug interaction is further complicated by that fact that many dietary supplement products are composed of a number of different botanicals (Kennedy and Seely, 2010; Pao *et al.*, 2012).

Pharmacodynamic Herb-Drug Interactions

A given constituent in a botanical can have an additive effect on a prescription drug, thus, potentiating the drug action at its effector sites. For example, valerian is an herb used as a sedative, particularly in the treatment of insomnia (Houghton, 1999). Valerian's effects are mediated through modulation of GABA neurotransmission and receptor function (Ortiz *et al.*, 1999), and the GABAergic effects of valerian on rat brainstem neuronal activities were reported (Yuan *et al.*, 2004a). In one clinical case report, valerian use was associated with an acute benzodiazepine-like withdrawal syndrome following surgery, and his symptoms were attenuated by benzodiazepine administration (Garges *et al.*, 1998).

Similar to valerian, kava may also act as a sedative/hypnotic by potentiating GABA inhibitory neurotransmission (Yuan *et al.*, 2002). Kava increased barbiturate sleep time in experimental animals (Jamieson *et al.*, 1989), an effect which may explain the mechanism underlying the report of a patient with coma attributed to a kava-alprazolam co-administration (Almeida and Grimsley, 1996), likely due to the pharmacodynamic interaction.

Pharmacokinetic Herb-Drug Interactions

Herbal constituents could affect absorption, distribution, metabolism, excretion, and toxicity (ADMET) of prescription drugs. This interaction is particularly clinically important when hepatic enzymes, which are responsible for catabolizing many drugs, are induced or inhibited (Bush *et al.*, 2007).

St. John's wort significantly increases the metabolism of many concomitantly administered drugs (Ernst, 1999). This significant effect is the result of the induction of cytochrome P450, 3A4 and 2C9 isoforms. Interactions with noticeable substrates of these isoforms are cyclosporine, indinavir, and warfarin. However, unlike prescription drugs, herbal pharmacokinetic data are largely unavailable for humans.

We previously evaluated the interactions between ginseng and warfarin in a controlled clinical trial (Yuan *et al.*, 2004b). We observed that ginseng significantly reduced warfarin's anti-coagulant effect by decreasing the value of the international normalized ratio (INR) and reducing plasma warfarin levels. Warfarin is eliminated extensively via the hepatic cytochrome P450 enzyme system (Kaminsky and Zhang, 1997) so it is possible that ginseng can enhance hepatic P450 enzyme function to increase the metabolism of warfarin.

Botanicals as Adjuvants for Cancer Chemoprevention

Botanicals have been the major source of therapy in many traditional medical systems and have also been used clinically for cancer patients (Yeung *et al.*, 2008; Yamaguchi *et al.*, 2011). Studies have reported that patients with cancer often resort to botanicals as a means to treat cancer-related symptoms, to reduce the adverse effects of chemotherapy, and possibly to increase the effects of chemotherapeutic agents (Shumay *et al.*, 2001; Ott, 2002; Randhawa and Alghamdi, 2011). In this section, ginseng again will be used as a model botanical, and discussion will be focused on colorectal cancer since this cancer is a leading cause of cancer related death in the U.S., and the second most prevalent cancer worldwide (Siegel *et al.*, 2012).

American Ginseng

Ginseng root has been used for thousands of years in Oriental medicine as a panacea that promotes health and longevity (Yun, 2003; Taira *et al.*, 2010; Chan *et al.*, 2011). American ginseng is a perennial plant native to eastern North America. The bioactive constituents of American ginseng, ginsenosides, are present in the root, leaf, stem and berry of the plant. More than 100 ginsenosides have been identified in American ginseng (Wang *et al.*, 2006a; Qi *et al.*, 2011a); chemical structures of representative ginsenosides are shown in Fig. 1.

American ginseng extracts were found to inhibit the growth of breast cancer cells (Corbit *et al.*, 2006). Our group showed that after steam treatment of ginseng, the antiproliferative effects on cancer cells were improved significantly, possibly due to the altered ginsenoside profile (Wang *et al.*, 2006b; Wang *et al.*, 2007).

Ginseng Enhances the Effects of 5-FU and Irinotecan in Human Colon Cancer Cells

5-FU (5-fluorouracil) and irinotecan are two chemotherapeutic agents widely used for colorectal cancer (Pinedo and Peters, 1988; Smorenburg *et al.*, 2006). We evaluated the synergistic tumoricidal effects of ginseng on 5-FU and irinotecan in various human colorectal cancer cell lines, SW-480, HCT-116 and HT-29. We observed that the ginseng extract significantly inhibited cancer cell growth in a concentration-dependent manner. Cell growth decreased more with the combined treatment of ginseng and 5-FU than with 5-FU alone, suggesting that ginseng, as a potential chemo-adjuvant, can reduce the dose of 5-FU needed to achieve desired effects and thereby decrease the dose-related toxicity of chemotherapy (Fig. 2) (Fishbein *et al.*, 2009; Li *et al.*, 2009b). Subsequently, this synergistic effect between panaxadiol, a purified ginseng component, and 5-FU has been demonstrated in the same settings (Li *et al.*, 2009a).

The reported treatment-related mortality and morbidity (such as neutropenia, nausea, vomiting, diarrhea, and asthenia) of irinotecan must be considered when using this agent (Vanhoefer *et al.*, 2001; Van Cutsem *et al.*, 2005). Thus, irinotecan is not usually considered a first-line medicine and is more frequently used in combination with 5-FU as a therapy for metastatic colorectal cancer (Cunningham *et al.*, 2001; Vanhoefer *et al.*, 2001). If ginseng compounds can synergistically enhance the activity of irinotecan, a dose reduction of the latter could possibly reduce dose-related adverse events. As shown in Fig. 3, the

combination of panaxadiol and irinotecan significantly enhanced antiproliferation in HCT-116 cells.

Underlying Mechanisms of Chemoprevention

To explore the mechanisms of action, we evaluated the effects of irinotecan and/or panaxadiol on cell cycle profile, induction of apoptosis, expression of caspases, and docking analysis. Because the combined use of irinotecan and panaxadiol significantly upregulated the expression of caspase 3, the Surflex-Dock program was used to determine the binding sites of panaxadiol and irinotecan to caspase 3. The binding affinities of test compounds to different binding sites were also determined, along with the locations of the hydrogen bonds formed (Du *et al.*, 2012).

Cell cycle analysis data showed that panaxadiol arrested cancer cells in the G1 phase, while 5-FU affected the cells in the S phase and/or the G2/M phases. These different cell cycle phases between the two test compounds could be considered as the basis of their synergistic action. This result can also be compared to those of panaxadiol and irinotecan: panaxadiol arrested cancer cells again in the G1 phase, while irinotecan affected the cells in the G2/M phases (Fig. 4).

Effects of panaxadiol and irinotecan on cancer cell apoptosis are shown in Fig. 5. The combination of panaxadiol and irinotecan significantly increased the percentage of apoptotic cells compared with irinotecan alone. Increased caspase 3 and caspase 9 activities were observed after treatment with both compounds, suggesting that the apoptosis was caspase-related cell death. The synergistic apoptotic effects were also supported by docking analysis, which demonstrated that panaxadiol and irinotecan bound two different chains of the caspase 3 protein (Du *et al.*, 2012).

Intestinal Microbiota Metabolites of Ginseng Compounds

After ingestion, ginseng is metabolized extensively by intestinal microbiota (Hasegawa *et al.*, 1996; Wang *et al.*, 2011c). Fig. 6 illustrates a metabolic pathway of ginseng saponins (Qi *et al.*, 2011b). There are deglycosylation reactions by gut microbiota via stepwise cleavage of the sugar moieties. The figure also shows that ginsenosides Rb1 and Rd are metabolized to compound K (Lee *et al.*, 2009). After 10 g of ginseng root ingestion by human volunteers, ginsenoside Rb1 was transformed to Compound K by intestinal microbiota, and plasma Compound K concentrations steadily increased four hours after ginseng ingestion along with the decrease of Rb1 levels (Dougherty *et al.*, 2011; Wang *et al.*, 2011a).

As an active ginsenoside metabolite, compound K exerts significant cancer chemoprevention activity (Kim *et al.*, 2009). We compared the chemopreventive effects of ginsenoside Rb1 and compound K in colorectal cancer cells. Compound K, which inhibited G1 progression and increased cell apoptosis, showed significant antiproliferative effects on the cells at 30 μ M, while Rb1 did not inhibit activity at 100 μ M (Wang *et al.*, 2012). In a separate study, using an AOM/DSS *in vivo* mouse model with Western diet (containing 20% fat), oral ginseng ingestion inhibited drug induced colitis and colonic tumorigenesis (Dougherty *et al.*, 2011). It appears that Compound K played an important role in the observed effects.

Other herbal medicines, such as astragalus (Santos *et al.*, 2011) and turmeric (Qi *et al.*, 2010) also have been reported as potential adjuvants for cancer therapeutics. It is possible the metabolites, not just the parent compounds, of these botanicals are important in their pharmacological activities.

Botanicals Reduce Chemotherapy-Induced Nausea and Vomiting

Cisplatin, a commonly used chemotherapeutic agent, causes significant nausea and vomiting. We tested whether pretreatment with American ginseng and one of its active antioxidant constituents, ginsenoside Re, could counter cisplatin-induced emesis using a rat pica model (reflecting nausea and vomiting in the rat). A significant dose-response relationship was observed between increasing doses of pretreatment with ginseng and reduction in cisplatin-induced pica. Pretreatment with ginsenoside Re also significantly decreased pica (Mehendale *et al.*, 2005). *In vitro* studies demonstrated a concentration-response relationship between ginseng and its antioxidant ability (Mehendale *et al.*, 2005). Thus, ginseng has a potential value for the treatment of chemotherapy-induced nausea and vomiting.

In addition to ginseng, ginger, grape seed, *S. baicalensis*, and *Ganoderma lucidum* have been reported to be effective in the treatment chemotherapy-induced nausea and vomiting in preclinical studies (Aung *et al.*, 2003; Wang *et al.*, 2005; Haniadka *et al.*, 2011).

Summary

Co-administration of herbal medicines and prescription drugs may induce negative outcomes via pharmacodynamic and pharmacokinetic herb-drug interactions. On the other hand, herbs and their metabolites may also enhance the effects of chemotherapeutic agents via synergistic activities. This potentiation of chemotherapy by botanicals was supported by cancer cell cycle and apoptotic observations. In addition, using computer-based docking model, botanicals and chemotherapeutic agents may occupy different binding sites, providing further evidence of their synergistic actions. Botanicals may also be potentially used to reduce chemotherapy-induced nausea and vomiting to improve patients' quality of life and to allow their subsequent chemotherapy. Controlled clinical studies are needed to verify the clinical utility of the botanicals.

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Figure 1.

Chemical structures of representative ginsenosides characterized from American ginseng. Two major groups of ginsenosides are listed. PPD: protopanaxadiol; PPT: protopanaxatriol; G: ginsenoside; Q: quinquenoside; F: floralquinquenoside. Adapted from (Qi *et al.*, 2011a).

Figure 2.

Synergistic antiproliferative effects of ginseng extract and 5-FU in human HCT-116 colorectal cancer cells. Cell growth decreased significantly with the combined treatment of ginseng extract (0.2 and 0.3 mg/mL) and 5-FU (10, 50 and 100 μM) than with 5-FU alone. Ctrl: control; GE: ginseng extract. *, $P < 0.01$ vs. corresponding groups of 5-FU only. Adapted from (Fishbein *et al.*, 2009).

Figure 3.

Panaxadiol enhances antiproliferative effects of irinotecan in HCT-116 cells. The combination of panaxadiol and irinotecan significantly enhanced antiproliferative effects in the cells. PD: panaxadiol; IRN: irinotecan. *, $P < 0.05$; **, $P < 0.01$, vs. corresponding groups of IRN only. Adapted from (Du *et al.*, 2012).

Figure 4.

Effects of irinotecan and panaxadiol on cell cycle in HCT-116 cells. (A) Representative histograms of cell cycle distribution. (B) Percentage of each cell cycle phase with various treatments or with control. PD: panaxadiol; IRN: irinotecan. Adapted from (Du *et al.*, 2012).

Figure 5.

Effects of irinotecan and panaxadiol on HCT-116 cell apoptosis and expression of caspases 3 and 9. (A) Representative scatter plots of PI (y-axis) vs. annexin V (x-axis). (B) Irinotecan and/or panaxadiol on expression of caspases 3 and 9. Cells were treated with irinotecan 10 μ M and/or panaxadiol 10 μ M. Ctrl: control; PD: panaxadiol; IRN: irinotecan. * $P < 0.05$ vs. corresponding control groups. Adapted from (Du *et al.*, 2012).

Figure 6.

Metabolic pathways of ginsenoside Rb1. “ $\rightarrow$ ” denotes major pathways; “ $-\rightarrow$ ” denotes additional pathways. [P]: metabolites detected in plasma; [U]: metabolites in urine; [F]: metabolites in feces; [B]: metabolites in bile. ig: metabolites after oral administration; iv: metabolites after intravenous injection. Compound K (C-K) is a pharmacologically active ginsenoside metabolite. Adapted from (Qi *et al.*, 2011b).