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Especial sobre Interacción de Productos Naturales y Fármacos / Special Issue on Natural Products and Drug Interactions

Use of natural products in anti-cancer alternative therapy: risk of interactions with conventional anti-cancer drugs

[Uso de productos naturales como terapia alternativa anti-cancerosa: riesgos de interacciones con fármacos anti-cancerosos convencionales]

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Abstract

Many cultures have used plants to treat medical affections and a percentage of modern medicines are obtained from plants. Today, several herbals have been screened for anticancer activity and many patients with cancer take plant extracts in addition to chemotherapy. This review offers an overview of the knowledge about the use of herbals and derivatives as a viable anticancer alternative therapy and their interactions (particularly, modulation of P-450 system and P-glycoprotein) with conventional anti-cancer drugs. It is suggested that health care professionals and patients should be aware of the potential for adverse interactions of this products with the anti-cancer drugs.

Keywords: Natural products, Anti-cancer drugs, Herbal-drug interaction.

Resumen

Muchas culturas han usado las plantas para tratar afecciones médicas y un porcentaje de las medicinas modernas son obtenidas a partir de las plantas. Hoy en día varias hierbas han sido usadas para el tratamiento del cáncer y muchos pacientes con cáncer toman extractos de plantas en adición a al quimioterapia. Esta revisión ofrece una panorámica del conocimiento acerca del uso de las hierbas y sus derivados como una terapia alternativa viable para el cáncer y sus interacciones (particularmente, en la modulación del sistema P-450 y la glicoproteina-P). Es recomendado que los profesionales de la salud y los pacientes estén atentos al potencial de interacciones adversas de estos productos con las drogas antitumorales.

Palabras clave: Productos naturales, Fármacos anti-cancerígenos, Interacción fármaco-hierba.

INTRODUCTION

Every culture throughout history has used plants to treat medical problems. Originally, the specific utility of herbs was assumed to be based on their shape or colour. Today in most of the developing world, plant remedies are the most prevalent treatments, with recipes handed down from generation to generation. Within the last decade there has been a dramatic increase in the sale and use of herbal and food supplements by Western populations and within the UK (Ritchie**,** 2007).

The use complementary and alternative medicine (CAM) by patients with cancer and survivors has been widely studied. Most patients use CAM to 'complement' the conventional therapies of radiotherapy, chemotherapy and surgery. Health professionals in general have expressed positive views when CAM is used 'complementarily' and not as an 'Alternative'. Results so far published have shown that CAM can contribute to improving the quality of life of cancer patients and their general well-being (Adams and Jewell, 2007) and CAM modalities play a role in supportive care and cancer (Leis and Millard, 2007). For example, today, this kind of therapy is used in many countries of the world, including development countries (Wolf et al., 2006; Simon et al., 2007; Tovey et al., 2006; Montazeri et al., 2007). Not only adult but paediatric cancer patients have used CAM too (Gomez-Martinez et al., 2007; Lim et al., 2006; Karadeniz et al., 2007; Gözüm et al., 2007).

However, the use of CAM in combination with conventional chemotherapeutics has incremented significantly risk for adverse effects, particularly due the narrow therapeutic index of many anti-cancer drugs. Besides, clinical data about pharmacokinetic (PK) interactions of CAM with chemotherapeutic drugs are few, it is suggested that CAM–anticancer drug interactions contribute significantly to the inter-individual variations in PK and clinical problems of unexpected toxicities and under-treatment seen in cancer patients (Marchetti et al., 2007). Patients taking chemotherapeutic drugs and CAM, at least 27% were at risk for developing clinically relevant CAM–drug interactions (Welder et al., 2006). Thus, the consequences of CAM–drug interactions are, a new focus of attention during the pre-clinical and clinical investigations of the chemotherapeutic agents. The objective of this item is to substantially review some preclinical and clinical data on phytochemicals, in terms of their effects as a potential treatment of cancer and their observed interactions with standard therapies.

USE OF NATURAL PRODUCTS BY PATIENTS WITH CANCER AND KNOWN DRUG INTERACTIONS

Plants have played an important role as a source of effective anti-cancer agents, and it is significant that over 62% of currently used anti-cancer agents are derived in one way or another from natural sources, including plants, marine organisms and micro-organisms (Fig. 1; Gonzales and Valerio, 2006).

Among the promising bioactive food components being investigated at the National Cancer Institute in prevention clinical trials to reduce cancer risk are indole-3-carbinol, sulforaphane, phytoestrogen isoflavones, perillyl alcohol, and green tea polyphenols among others (Table 1; Greenwald, 2004).

Sulforaphane (SF)

Preclinical and clinical evidences. Epidemiological studies suggest that a diet rich in broccoli can reduce the risk of cancer at several sites, including the prostate, lung, breast and colon (Juge et al., 2007). The anticarcinogenic activity has been largely attributed to the biological activity of SF, the isothiocyanate derived from 4-methylsulphinylbutyl glucosinolate, which accumulates in broccoli (Gasper et al., 2007). SF modulates many cancer-related events, including susceptibility to carcinogens, cell death, cell cycle, angiogenesis, invasion and metastasis (Zhang and Tang, 2007; Fimognari and Hrelia, 2007). It has been reported in many studies that SF suppresses the growth of some tumoral cells lines (Chuang et al., 2007; Matsui et al., 2007; Mi et al., 2007; Park et al., 2007; Pledgie-Tracy et al., 2007; Shan et al., 2006; Pappa et al., 2007a). These findings suggest that cell vulnerability to SF-mediated apoptosis is subject to regulation by cell-cycle-dependent mechanisms (Fimognari et al., 2007). Other study provides that SF also acts to inhibit angiogenesis via suppression of endothelial cell proliferation (Jackson et al., 2007). Although, in clinical studies there were not that advances, a formal phase I study of safety, tolerance and pharmaco-kinetics was carried out (Shapiro et al., 2006). No recent drug interactions or medical contraindications with the use of SF have been reported.

Epigallocatechin-3-gallate (EGCG)

Preclinical and clinical evidences. Green tea polyphenols are considered beneficial to human health, especially as cancer chemopreventive agents. Some results in animal and epidemiological studies suggest that EGCG the most abundant polyphenol in green tea, could inhibit the invasion and migration of human oral and colon cancer cells and that the effects may partially because of the decreased productions of MMP-2, MMP-9 and uPA (Ho et al., 2007). It is demonstrated that EGCG can inhibit the growth of some cancer cell lines, including hepatocellular carcinomas cell lines HLE, HepG2, HuH-7 and PLC/PRF/5 through the induction of cell-cycle arrest (Nishikawa et al., 2006), in ovarian carcinoma cell lines HEY and OVCA 433 (Spinella et al., 2006a,b), in human colorectal cancer cell lines HT-29 and HCA-7 (Hwang et al., 2007; Peng et al., 2006). Not only EGCG but other flavonoids such as quercetin and rutin have anticarcinogenicity and antitoxicity properties through inhibition of oxidative activation (Hu et al., 2006).

Effects on drug-metabolizing enzymes, P-glycoprotein and pharmacokinetic interactions: Muto et al. (2001) demonstrated that epigallocatechin gallate inhibit the *in vitro* activity of CYP1A1/2 and CYP3A4. Moreover, a general inhibition of several P-450s (CYP2A6, CYP2C19, CYP2E1) by epigallocatechin gallate has been observed, indicating a non-specific inhibitory effect.

Figure 1. Anti-tumor drugs approved from 1981-2002 (62% were of natural origin).

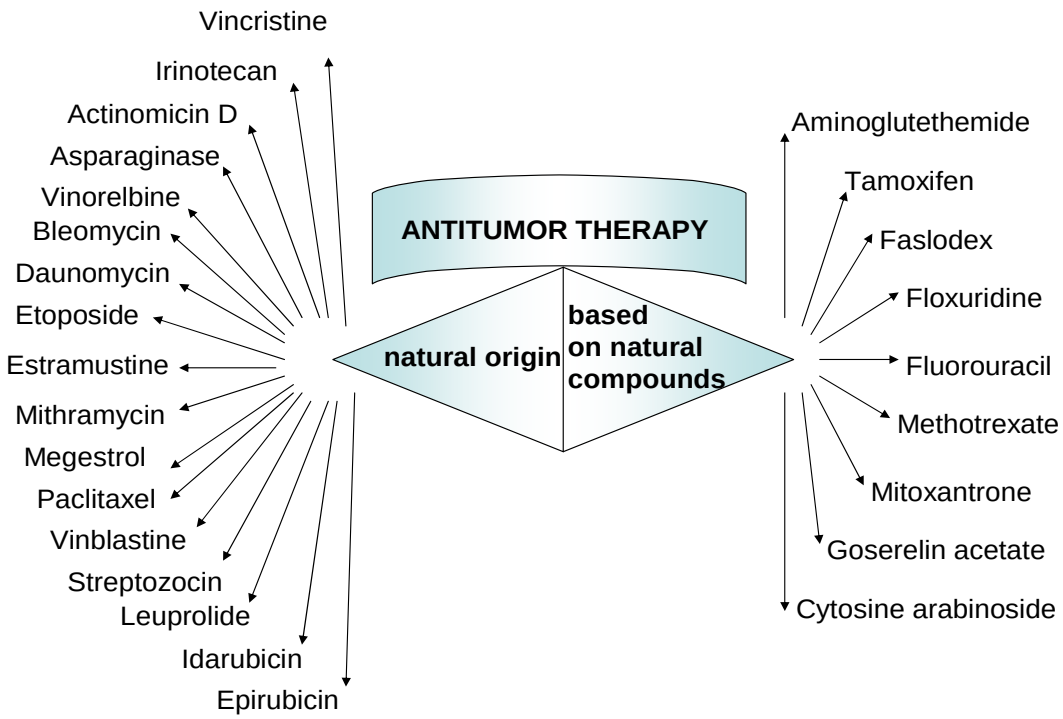


Table 1. Preclinical studies with natural products in cancer.

Herbal/Compound	Treatment
Scutellaria baicalensis	Glioma and colon cancer.
Garlic (*Allium sativum*)	Prostate, glioblastoma and colon cancer.
Saw Palmetto (*Serenoa repens)*	Prostate and ovarian cancer.
Curcumin	Intestinal, prostate, breast, colon, glioma, prostate and ovarian cancer.
Indole-3-carbinol	Melanoma, colon, prostate, breast and bone metastasis of breast cancer.
Caffeic acid phenethyl ester	Glioma and colon cancer.
Epigalocatechin-3-gallate	Hepatocellular carcinomas, ovarian carcinoma and colorectal cancer.
Genistein	Breast, prostate, bladder and neuronal cancer.
Sulforaphane	Osteosarcoma, prostate, lung, breast, colon, hepatocarcinoma, ovarian cancer and cervical carcinoma .
Licopene	Prostate, colon, human erythroleukemia and B chronic lymphocytic leukaemia.

The activation of benzo(a)pyrene, 2-amino-1-methyl-6-phenyl-imidazole-(4,5-b)pyridine and aflatoxin B-1 by recombinant CYP1A1/2 and CYP3A4, respectively,was also inhibited by this molecule. These effects have been associated with the chemopreventive properties of catechins observed in rodents. The potential interactions of green tea catechins on the metabolic activation of irinotecan, a prodrug directed to the treatment of metastatic colorectal cancer have been suggested (Mirkov et al., 2007). Recently, a heteroactivation of CYP1A1 by teas and tea polyphenols was observed, which supports the hypothesis that this mechanism of CYP1A1 activation may be part of the explanation for the lack of epidemiological support for cancer prevention observed by tea (Nagle et al., 2006).

Genistein (Gen)

Preclinical and clinical evidences. Gen, found at high levels in soybeans and soy foods (Meeran and Katiyar, 2008), is a controversial candidate cancer preventive phytochemical whose effects on prostate (Perabo et al., 2008) and breast cancer cells have been the most studied (Lavigne et al., 2007; Moiseeva et al., 2007). The genistein metabolite, 5,7,3',4'-tetrahydroxyisoflavone, induced G2-M cell cycle arrest in T47D tumorigenic breast epithelial cells (Vauzour et al., 2007). Genistein has been shown to inhibit human prostate cancer (PCa) cell motility (Craft et al., 2008). Some studies suggest that Gen may be a promising chemopreventive agent against androgen-dependent and independent PCa (Wang et al., 2007). *In vitro* studies have shown induction of apoptosis and inhibition of cell growth in androgen-sensitive and androgen-independent cell lines (Vaishampayan et al., 2007). But, Gen also *in vivo* decreases the proliferative potential, retards cancer progression and maintains the integrity of the prostatic epithelial cells (El Touny and Banerjee, 2007). Not only Gen but other bioactive flavonoid (baicalein) (Chao et al., 2007) and dietary isoflavones (biochanin A and daidzein) have been related to anticancer activity on bladder, breast and neuronal cancer respectively (Moon et al., 2007; Lo et al., 2007). Even, a study carried out by Nagata et al. (2007) showed Gen and daidzein were significantly associated with decreased risk of prostate cancer in Japanese men.

Effects on drug-metabolizing enzymes, P-glycoprotein and pharmacokinetic interactions: Genistein and daidzein interact with transporters such as P-gp and the canalicular multispecific organic anion transporter (Evans, 2000). Genistein inhibit P-glycoprotein-mediated efflux of paclitaxel, and its oxidative metabolism catalyzed by CYP 3A4 and 2C8 (Li and Choi, 2007). Biochanin A and formononetin are converted to genistein and daidzein in human microsomes, respectively. Daidzein is a competitive inhibitor of CYP1B1 and genistein exhibited mixed inhibition (Roberts et al., 2004).

Curcumin (Cur)

Preclinical and clinical evidences: Cur is a polyphenolic compound derived from dietary Asian spice turmeric (*Curcuma longa* L.), particularly across the Indian subcontinent (Gradisar et al., 2007). It possesses diverse pharmacologic effects including, immunomodulators (Ferguson and Philpott, 2007), antiproliferative (Karunagaran et al., 2007) and antiangiogenic activities (Anand et al., 2007). Cur has been shown to protect against skin, oral, intestinal, prostate, breast and colon carcinogenesis (Surh and Chun, 2007). It has been reported in many studies that Cur suppresses growth of some tumoral cells lines (Shankar et al., 2007; Shankar and Srivastava, 2007; Deeb et al., 2007; Liu et al., 2007; Dhandapani et al., 2007; Mitra et al., 2006; Cao et al., 2007; Xia et al., 2007; Yoon and Liu, 2007). In addition, a recent completed phase II clinical trials suggests that Cur may prove to be useful for the chemoprevention of colon cancer in humans (Johnson and Mukhtar, 2007).

Effects on drug-metabolizing enzymes, P-glycoprotein and pharmacokinetic interactions: Curcumin inhibited CYP1A2, CYP2C9, CYP2D6, CYP3A4 and CYP2B6 (Appiah-Opong et al., 2007a). Curcuma drugs might inhibit the catalytic activity of intestinal CYP3A4 (Hou et al., 2007) and recombinant human CYP1A2, CYP3A4, CYP2B6, CYP2C9 and CYP2D6 were inhibited *in vitro* (Appiah-Opong et al., 2007b). Results demonstrate that curcuminoids effectively inhibit MRP1-mediated transport (Chearwae et al., 2006) and also mediate down-regulation of intestinal P-gp (Zhang et al., 2007).

Indole-3-carbinol (I3C)

Preclinical and clinical evidences: I3C, a naturally occurring component of Brassica vegetables, such as cabbage, broccoli, and Brussels sprouts, induces a G1 cell cycle arrest of human breast cancer cells (Jump et al., 2007). I3C could inhibit bone metastasis of breast cancer by inhibiting CXCR4 and MMP-9 expression mediated via the inhibition of the NF-kappaB signaling pathway (Rahman et al., 2006). However, other studies have shown that I3C can induce apoptosis in G361 human melanoma cell (Kim et al., 2006) and in LNCaP prostate cancer cell (Hsu et al., 2006). Not only I3C but its condensation product 3,3'-diindolylmethane are acting by cytostatic mechanisms in human colon cancer cell lines (Pappa et al., 2007b). Furthermore, have been completed a phase I trial in women of the proposed chemopreventive activity that I3C could present (Reed et al., 2006) and also in women with histologically confirmed high-grade of vulvar intraepithelial neoplasia, which showed the potential therapeutic benefits of I3C. Meanwhile, more clinical and scientific investigations are required to support these findings (Naik et al., 2006).

Effects on drug-metabolizing enzymes, P-glycoprotein and pharmacokinetic interactions: The potential of I3C to modulate P-gp expression was evaluated in vinblastine (VBL)-resistant K562 human leukemic cells (Arora et al., 2005). Other results indicate that I3C could be used as a novel modulator of P-gp-mediated multidrug resistance *in vitro* and may be effective as a dietary adjuvant in the treatment of cancers.

Garlic

Preclinical and clinical evidences: Garlic has long been used as a culinary spice and medicinal herb, cultivated in the Middle East and was first mentioned as medicine in China. Early trials suggested the potential of garlic to lower cholesterol and triglyceride levels in serum (Silgay and Neil, 1994; Warshafsky et al., 1993), but a recent trial has shown almost no benefit (Berthold, 1998). Garlic-derived organosulfur compounds induce apoptosis in many cancer cell lines (Lu et al., 2007) but not in Caco-2 and HT-29 cell lines (Jakubíková and Sedlák, 2006), human glioblastoma T98G and U87MG cells (Das et al., 2007) and some human prostate cancer cells (Kim et al., 2007; Xiao et al., 2006; Arunkumar et al., 2006). Garlic has also been shown to alter blood coagulation by increasing platelet aggregation and increasing fibrinolysis (Kiesewetter et al., 1990). Garlic has been used in a variety of conditions, including atherosclerosis, chronic candidiasis, hypertension, hyperlipidemia, hypertriglyceridemia, peptic-ulcer disease, peripheral vascular disease, and sicklecell anemia, and as a chemo-preventative agent for gastrointestinal tumors.

Effects on drug-metabolizing enzymes, P-glycoprotein and pharmacokinetic interactions: In vitro studies have shown that garlic constituents modulate the activity of various CYP isozymes. Extracts of garlic inhibit CYP2C9, CYP2C19, CYP3A4, CYP3A5 and CYP3A7 activity, whereas no effect on CYP2D6 was found (Foster et al., 2001; Chen et al., 2003). Rats treated with diallyl sulfide, diallyl disulfide, allylmethyl sulfide and allyl mercaptan had a suppression of CYP2E1 activity as a result of competitive inhibition (Brady et al., 1991; 1988; Haber et al., 1994; Kwak et bal., 1994; Kwak et al., 1995; Reicks and Crankshaw, 1996; Guyonnet et al., 2000; Yang et al., 2001). In addition, diallyl sulfone is known to be a suicide inhibitor of CYP2E1 (Jin and Baillie, 1997). However, long-term administration led to enhanced activity and increased expression of CYP1A, CYP2B (Chen et al., 2003; Sheen et al., 1999; Dalvi, 1992) and CYP3A (Wu et al., 2002). Studies using *in vitro* and *in vivo* animal models have also indicated that various garlic constituents used at high concentrations can induce CYP3A4 activity (Raucy, 2003) and conjugating enzymes (Kwak et al., 1994; Guyonnet et al., 1999; Wargovich et al., 1992; Munday and Mundsay, 1999).

Reports suggest that CYP2E1 activity is also inhibited in humans receiving garlic for four weeks (Gurley et al., 2002). Clinical studies have shown that garlic no affect the activity of CYP1A2, CYP2D6 and CYP3A4 (Markowitz et al., 2003). Two trials indicated that it significantly decreases the systemic exposure to the HIV protease inhibitors saquinavir (Piscitelli et al., 2002) and ritonavir (Gallicano et al., 2003), which are metabolized by CYP3A4 (Fitzsimmons and Collins, 1997) and substrates for P-glycoprotein (Kim et al., 1998).

Saw Palmetto

Preclinical and clinical evidences: Saw palmetto (*Serenoa repens*) is a small low-growing palm tree native to southeastern North America. Saw palmetto is used in men with the hope of toning and strengthening the reproductive system, and

specifically for symptoms of prostate enlargement (Shi et al., 2008). The main constituents of saw palmetto include carbohydrates, fixed oils, steroids, flavonoids, resin, tannin, and volatile oil (Sorenson and Sullivan, 2007). It has been reported that saw palmetto can inhibit prostate cancer proliferation. In women, the principal use of saw palmetto is to reduce ovarian enlargement and to increase the size of small, undeveloped mammary glands (Ernst, 2002). No drug interactions or medical contraindications with the use of saw palmetto have been reported, meanwhile, it would be prudent to avoid concomitant use with other hormonal therapies (eg, estrogen replacement therapy and oral contraceptives), which may provide an additive effect.

Mangifera indica (Vimang)

Preclinical and clinical evidences: Vimang is a nutritional supplement obtained from stem bark of *Mangifera indica* L. (mango). This aqueous extract is used in Cuba in presumably healthy people with environmental, nutritional risk factors, or population with chronic diseases to increment the quality of life through the increase of antioxidant mechanisms (Garrido-Garrido et al., 2007). Ethnomedical studies lead to a great improvement of quality of life in patients with cancer (Tamayo et al., 2001). Preclinical studies have demonstrated anti-angiogenic effects of Vimang in different cell lines (unpublished data). The active ingredient of Vimang formulations consists on a defined mixture of polyphenols, terpenoids, steroids, fatty acids and microelements that imparts unique properties to these formulations like antioxidant supplement (Núnez et al., 2002).

Effects on drug-metabolizing enzymes, P-glycoprotein and pharmacokinetic interactions: Studies performed using rat hepatocytes culture showed Vimang did not modify CYP2C, 2D1, 2E1 and 3A1 activities, but it changed oxidations catalyzed by CYP1A2 and 2B1. It also reduced CYP1A2 activity, which may be caused either by a reduction of CYP1A2 levels induced by Vimang or by direct interaction of some component(s) of the extract with the catalytic function of the enzyme. The marked concentration-dependent decrease in CYP1A2 activity observed in hepatocytes shortly incubated with Vimang revealed a direct interference at the activity level (Rodeiro et al., 2007).

Subsequent studies using human microsomes permitted to confirm previous findings on CYP1A activity observed on rat hepatocytes, but inhibition on human CYP3A activity was found. This apparent discrepancy could be due to different catalytic properties of rat CYP3A1 and human CYP3A4, and/or to differences in the metabolism of Vimang components in both species. No drug interactions with the use of Vimang have been reported, meanwhile, the *in vitro* results suggest that potential interactions with anticancer drugs metabolized for these isoforms must be considered.

Others

Scutellaria baicalensis (SB) is a Chinese herbal medicine historically used in anticancer therapy. Baicalin is the major anti-cancer component of SB (Kumagai et al., 2007). They inhibit the growth of H460 human lung nonsmall carcinoma cell line (Leung et al., 2007), LNCaP and PC-3 human prostate cancer cell lines (Ye et al., 2007) and malignant glioma cells (Scheck et al., 2006). Not only SB but other herbs such as, *Artemisia annua* (Chinese wormwood), *Viscum album* (European mistletoe), resveratrol and proanthocyanidin (grape seed extract), *Magnolia officinalis* (Chinese magnolia tree), *Ginkgo biloba*, quercetin, *Poria cocos*, *Zingiber officinalis* (ginger), *Panax ginseng* (ginseng), *Rabdosia rubescens* hora (Rabdosia), and *Chinese destagnation* herbs can enhance the efficacy of the conventional therapies or reduce toxicity (Sagar et al., 2006a), can inhibit angiogenesis (Yance and Sagar, 2006), tumour progression and reduce the risk of metastasis (Sagar et al., 2006b). The aqueous extract of *Scutellariae baicalensis* Georgi has inhibitory activity against P-gp 170, a multiple drug resistant gene product. Baicalein, one of the major flavones, was found to be responsible for this activity (Lee et al., 2004). In contrast, grapefruit juice inhibits intestinal CYP3A4 (Fattinger and Meier, 2002).

Caffeic acid phenethyl ester (CAPE), an active component of propolis, has been implicated in the regulation of cell growth and apoptosis in SW480 (He et al., 2006) and HCT116 human colon cancer cells *in vitro* (Xiang e al., 2006) and C6 glioma cells *in vivo* (Tseng and Lee, 2006). Recently, two new propolis-derived prenylflavanones (propolin A and propolin B) showed also induce apoptosis (Chen et al., 2007). CAPE and other plant-derived polyphenols such as, resveratrol, silymarin, flavopiridol, emodin, piperine, oleandrin, ursolic acid, and betulinic acid can sensitize tumor cells and inhibit pathways that lead to cancer treatment resistance (Garg et al., 2005).

Figure 2. ATP-binding cassette drug transporters involved in the transport of chemotherapeutic drugs.

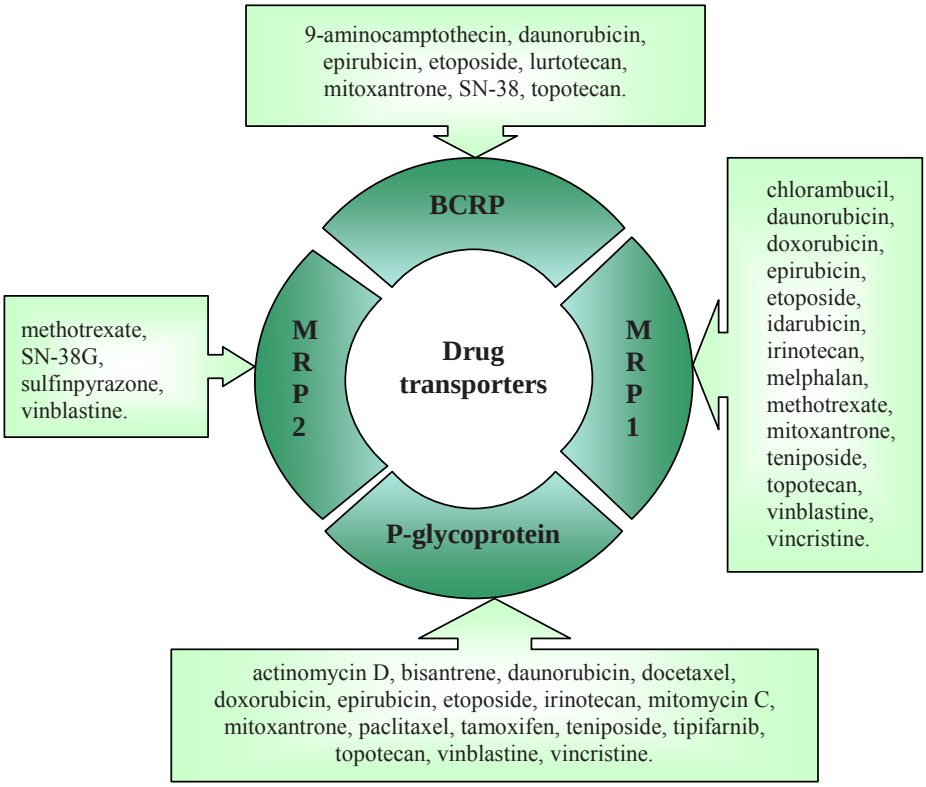
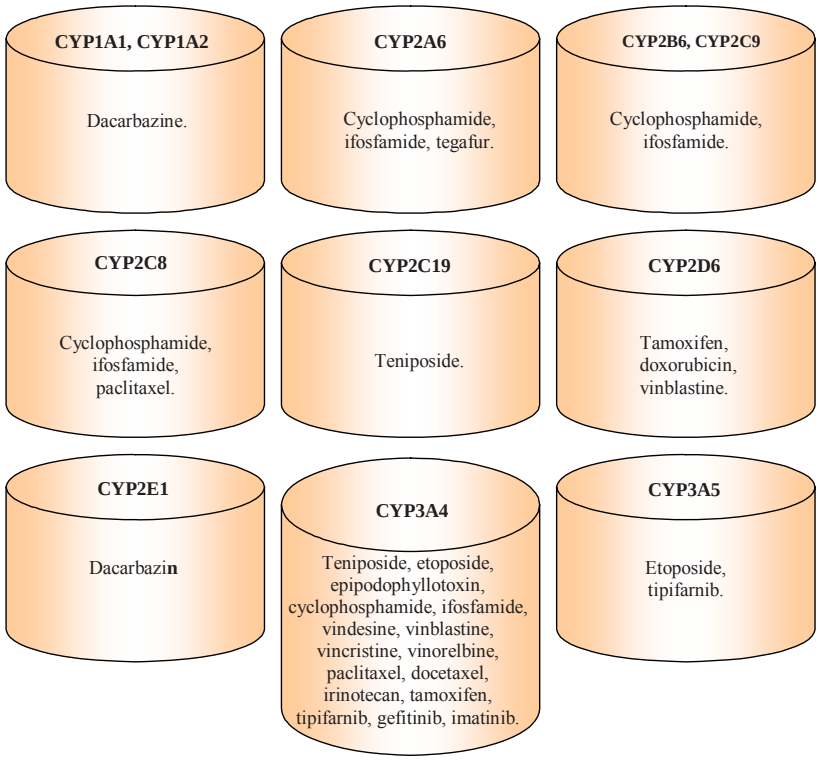


Figure 3. Metabolizing enzymes involved in the metabolism of chemotherapeutic drugs.



Tomatoes (*Lycopersicon esculentum* Mill.) are the principal dietary source of lycopene (Lic), which is one of carotenoid and is highly beneficial in preventing some diseases such as the cancer (Wan et al., 2007). Lic has been suggested the most promising agents for decreased prostate cancer risk (Thompson, 2007; Peters et al., 2007; Von Löw et al., 2007; Jian et al., 2007) and it can affect growth of different human tumour cell lines (Palozza et al., 2007; Salman et al., 2007). Although, in 2004, the U.S. Food and Drug Administration (FDA) found no credible evidence to support an association between Lic intake and a reduced risk of prostate, lung, colorectal, gastric, breast, ovarian, endometrial, or pancreatic cancer and also found no credible evidence for an association between tomato consumption and a reduced risk of lung, colorectal, breast, cervical, or endometrial cancer (Kavanaugh et al., 2007).

Herbal remedies with the potential to modulate cytochrome P-450 activity and thus participate in interactions with conventional drugs include Milk thistle, *Angelica dahurica*, ginseng, Danshen and liquorice (Ioannides, 2002).

Clinical relevance of natural products–anticancer drug interactions

An increasing number of cancer patients are using CAM in combination with their conventional chemotherapeutic treatment. Therefore patients who are subjected to combination treatments face considerable risk of drug-drug interaction. Importantly, although there are plenty of experimental data available, large epidemiological trials to underline the antitumoral effects of natural products-anticancer drug combination are scarce. Hence, if potential drug interactions are to be predicted, it is essential that the ability of herbal products to interfere with drug-metabolizing enzyme systems is fully established.

Most of the herbal formulations or pure compounds extracted from herbals are known to enhance the cytotoxic effect of drugs through different mechanisms. For example, the polyphenol mangiferin, a C-glucosylxanthone, potentiates cisplatin-, vincristin-, doxorubicin-, etoposide-, adriamycin- and araC-mediated cell death through suppression of NF-κB activation (Sarkar et al., 2004). An additive antiproliferative effect was note with the combination of genistein, a soy derived phytoestrogen, and tamoxifen on cancerous breast cells (Tanos et al., 2002).

Another example of the effect of CAM on the pharmacokinetic of anticancer drugs is St John's Wort (SJW, *Hypericum perforatum*). In cancer patients using SJW, a widely used herbal product, in combination with irinotecan, the plasma levels of SN-38, the active metabolite of irinotecan, were 42% lower (Mathijssen et al., 2002).

Chemoprevention by edible phytochemicals is now considered to be an inexpensive, readily applicable, acceptable and accessible approach to cancer control and management but more study is warranted.

The clinical importance of herb-drug interactions depends on many factors associated with the particular herb, drug, drugs transporters (Fig. 2) and drugs metabolizing enzyme (Fig. 3). Herbs should be appropriately labelled to alert consumers to potential interactions when concomitantly used with drugs and to recommend a consultation with their general practitioners and other medical carers (Hu et al., 2005).

CONCLUSIONS

We here shown the rich variety of natural products related with cancer prevention and treatment. As the intake of CAM is increasing, extra care must be taken with the consumption of these products when using coventional cancer treatments as the wide molecular mechanisms they can target may interact with those of the standard therapies. It is a fact how many cancer patients use CAM and standard therapies together without the knowledge/advice of their healthcare providers.

Knowledge about how these products modulate the many metabolizing enzymes and/or drug transporters, which may lead tolower therapeutic efficacy and/or adverse effects of conventional drugs is limited. It is therefore important that physicians are aware of the possibility of CAM–drug interactions; more when the resultant action of it could are not known or not enough studied. Physicians must be prepared to discuss CAM use with their patients and to be aware of potential CAM–anticancer drug interactions without prejudices.

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