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REVIEW ARTICLE

Potential Synergism of Natural Products in the Treatment of Cancer

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Cancer is the second leading cause of death worldwide. There is thus increased interest in alternative treatment modalities that include chemotherapy, hormonal supplements, surgery, radiation therapy, complementary or alterative medicine, used alone or in combination. Therefore patients who are subjected to combination treatments such as hormonal supplements or alternative medicine face considerable risk of drug–drug interactions. The administration of herbal drugs by patients without a physician's prior counseling is increasing globally and there is a possibility of herb–drug interactions too. Herbal drugs or extracts themselves contain a combination of active constituents, which interact within themselves and also between other prescribed pharmaceutical drugs to either enhance (synergize) or decrease (antagonize) the therapeutic effect. This review focuses on a number of reports of herb–drug interactions, their mechanism of action with a special emphasis on dietetic phytochemicals such as quercetin, genistein, curcumin and catechins. All phytochemicals tend to increase the therapeutic effect by blocking one or more targets of the signal transduction pathway, by increasing the bioavailability of the other drug or, by stabilizing the other drug in the system. Copyright © 2006 John Wiley & Sons, Ltd.

Keywords: chemoprevention; phytochemicals; herb–drug interactions; curcumin; epigallocatechin gallate; quercitin; genistein.

INTRODUCTION

Historically plants have provided a source of inspiration for novel drug compounds and have shown great promise in the treatment of diseases. The great variety of secondary metabolites from plants have been sources of commercially important pharmaceutical compounds. Some 41% of newly approved drugs between the period 1983–1994 had a natural product origin and this increased to 60% when considering antiinfective and anticancer compounds (Cragg *et al.*, 1997). Initially natural products were used in unmodified form, as concentrated herbal extracts. It becomes a complex matter when using an herbal product, because its activity is not usually due to a single entity but due to a mixture of other constituents. For example, green vegetables and fruits were found to reduce greatly the risk of cancer, extensively due to the action of a combination of polyphenols (Mertens-Talcott and Percival, 2005). Some compounds might either enhance (synergistic) or decrease (antagonistic) the therapeutic activity or toxicity of drugs. This combined action of numerous biologically active compounds is due to varied types of herb–drug interactions and relatively less information is available in this field due to a lack of systematic data.

The study of interactions of herbs and drugs can be traced back thousands of years when herbs were combined with each other. Many safer, cocktails of herbs are used in the traditional methods of Chinese, Japanese Kampo and Indian Ayurveda. For example, in Chinese medicine, the common term used for interaction is 'Xiang Xu' literally meaning mutual or reciprocal action. Ayurveda also uses many fixed combination formulae with 'Trikatu' [a mixture of dried fruits of *Piper nigrum* Linn., *Piper longum* Linn. (Piperaceae) and the dried rhizomes of *Zingiber officinale* Roscoe (Zingiberaceae)] (Dash and Junius, 1987) or 'Rasayanas' which were combinations of herbs with immunomodulatory botanicals. This theme of multiple chemicals acting in a combined manner could be attributed to the fundamental role of secondary metabolites in promoting plant survival. They serve in plant defense mechanisms and ensure a decrease in the chance of developing resistance to pests and microorganisms.

There is an increased use of herbs along with conventional drugs rather than using them in place of drugs, raising concerns for the study of interaction of herbs and drugs. Four points can be put forward to explain the increased use of a combination of drugs.

First, the increase in the cost of health care, drug prices and the number of patients. Second an increase in multidrug resistant strains has led to a search for alternative modes of treatment. Third the decreased efficacy and treatment failure of modern drugs also favors the use of herbs. Finally, due to the complex multiple interconnected nodes of the cell signaling network, it is important to use multiple modulating strategies to achieve clinical success. Phytomedicines can achieve this strategy by exerting beneficial effects through additive or synergistic actions of several chemical compounds acting at single or multiple target sites associated with a physiological process.

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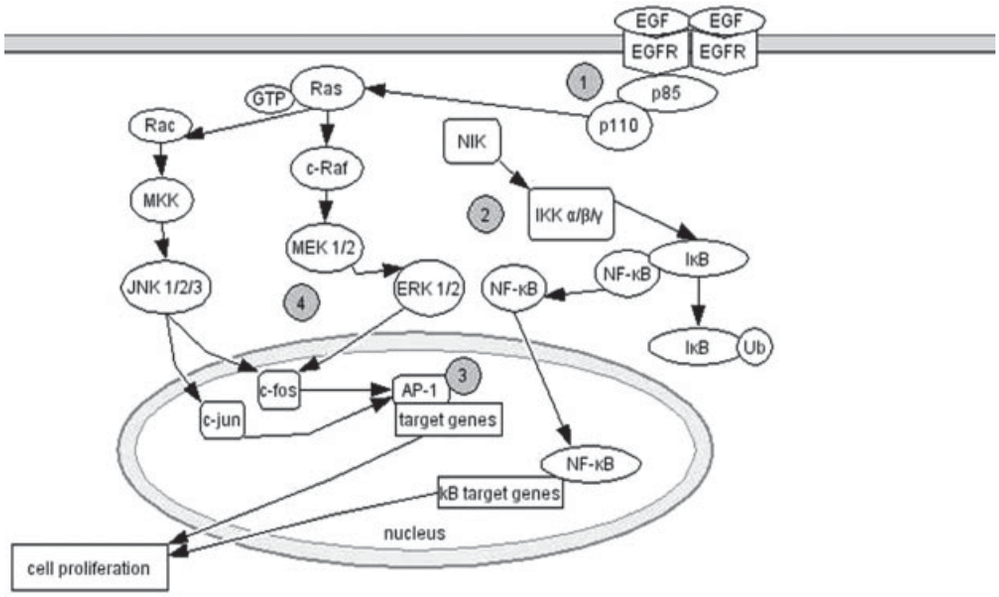

Figure 1. Molecular targets for the phytochemicals in cancer. [1-curcumin, genistein, resveratrol, catechins block the EGFR; 2-curcumin, catechins, silymarin, sanguinarine, emodin, resveratrol, capsaicin inhibit the NF-κB pathway; 3-curcumin, capsaicin, resveratrol, green tea catechins, 6-gingerol inhibit AP-1 pathway; 4-EGCG block the MAPK signaling pathway]. For additional details see text.

SIGNAL TRANSDUCTION AND CANCER

Modern man is confronted with an increasing incidence of cancer and it is the second leading cause of death after heart disease. Carcinogenesis is a multi-step process that proliferates in an unrestricted manner due to an imbalance between growth-promoting and growth-inhibiting mechanisms. An intricate network of signaling pathways is involved in these control mechanisms. The main focus of the current treatment regimes is to block potential points on key biochemical routes that result in the transformation of a normal cell into a cancerous cell. Some of the major signal transduction pathways in cancer that are commonly blocked by phytochemicals are briefly described below, as detailed description of these pathways is beyond the scope of this review.

AP-1 and NF-κB activation pathway

The NF-κB (nuclear factor-κB) pathway plays an important role in the pathogenesis of several important human inflammatory diseases including cancer, diabetes, rheumatoid arthritis and atherosclerosis (Baldwin, 2001). Binding of NF-κB dimers to target promoters initiates inflammatory and innate immune responses (Richmond, 2002). But NF-κB is sequestered in its inactive form in cytoplasm through interaction with IκB (Baeuerle, 1998). Phosphorylation of IκB by IκB kinase (IKK) (in turn phosphorylated by NF-κB inducing kinase – NIK) causes the degradation of IκB and the release of NF-κB. Subsequently NF-κB binds to specific κB binding sites in promoter sequences of several genes (Richmond, 2002) such as cyclin D1, apoptosis suppressor proteins such as Bcl-2 and Bcl-X_L and those required for metastasis and angiogenesis (Hanausek *et al.*, 2003). It is suggested that NF-κB activation promotes cell survival and proliferation mechanisms. Dysregulation of NF-κB pathways is crucial for the development of various types of cancer (Shishodia and Aggarwal, 2004).

NF-κB works in concert with other transcription factors such as activator protein-1 (AP-1) that regulates the expression of several genes associated with cell differentiation and proliferation. It is a complex of Jun and Fos (Eferl and Wagner, 2003) and promotes the expression of genes involved in angiogenesis and the invasive growth of cancer cells (Fig. 1).

RTK related pathways of signal transduction

Polypeptide growth factors, such as platelet derived (PDGF) and epidermal growth factors, can promote the tyrosine phosphorylation of cellular proteins (Cooper *et al.*, 1982). They interact with their specific receptors called receptor tyrosine kinases (RTKs) such as epidermal growth factor receptor (EGFR) HER2, HER3 and HER4 of subclass I (erb B) by sending a signal to the cells. Most of the human malignancies express high levels of growth factors and their receptors. RTK is essential for the activation of phospholipase C (PLC)-γ (to activate a cascade of intracellular signaling) (Margolis *et al.*, 1989) and signal transducers and activators of transcription molecules (STATS) (latent transcription factors) (Darnell, 1997). Constitutive overexpression of RTKs is involved in the pathogenesis of a variety of tumors. The tyrosine protein kinases have now emerged as one of the most important groups of drug targets, accounting for 20% to 30% of the drug discoveries of many pharmaceutical companies (Sodhi *et al.*, 2003) (Fig. 1).

MAPK signaling pathway

The signal transduction of the MAPK (mitogen-activated protein kinase) super family of protein kinases provides proliferative signals to the cells. Activation of various RTKs stimulates Ras, which in turn activates the protein kinase Raf-1. The latter further phosphorylates and activates MEK1/2 (MAP kinase kinase). MEK1/2 then phosphorylates the ERK 1/2

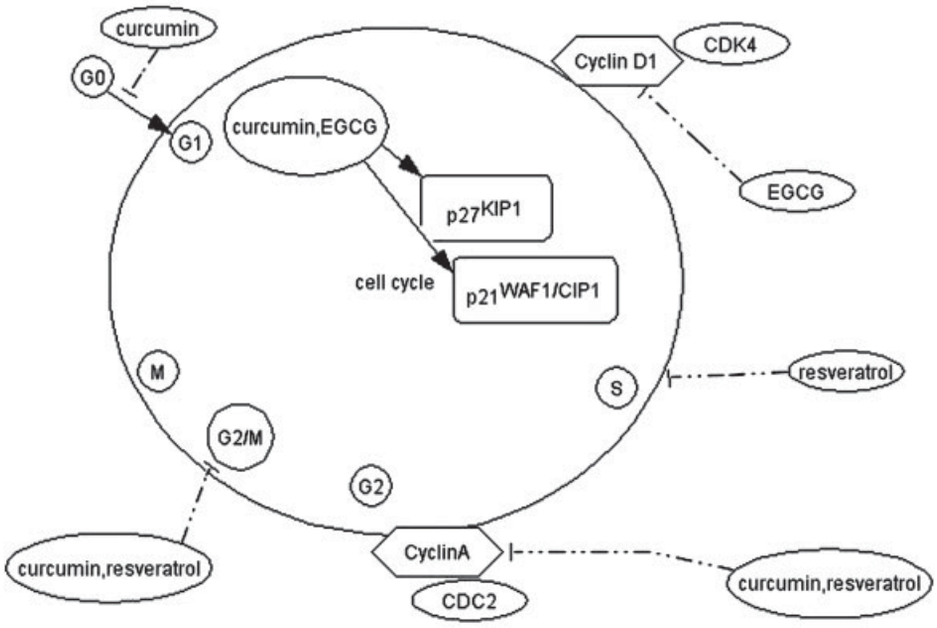

Figure 2. Phytochemicals as inhibitors of cell cycle. Broken lines indicate inhibition and continuous line indicated activation. [p27KIP1 and p21WAF1/CIP1 are CDK inhibitors].

(extracellular signal regulated kinase) pathway. In addition JNK 1/2/3 (c-Jun *N*-terminal kinase) and p38 $\alpha/\beta/\gamma$ pathways (belonging to the MAPK superfamily) also functions in parallel (Chang and Karin, 2001) (Fig. 1). Dysregulation of these MAPKs pathways are involved in a variety of tumors. Therefore targeting this pathway can be an effective strategy in cancer chemotherapy.

COX-2 and cancer

Inhibition of cyclooxygenase (COX), particularly the COX-2 isozyme, and blocking the prostaglandin (PG) cascade may have an impact on neoplastic growth and its development, by inhibiting proliferation, angiogenesis and metastasis. It is highly overexpressed in premalignant and malignant conditions in the colon, liver, pancreas, breast, lung, bladder, skin, stomach, head, neck and esophagus (Subbaramaiah and Dannenberg, 2003).

Regulation of cell cycle in cancer

Sequentially controlled and correctly oriented molecular steps in a cell cycle ensure the normal process of cell division. A disorder in this basic program causes cancer. The checkpoints in G_1 and G_2 phases make sure that the cell cycle proceeds in a regulated manner. The assembly and disassembly of a series of protein kinases such as CDK (cyclin dependent kinases) drive progression through the cell cycle. CDK activity is further regulated by other classes of proteins such as the Cip/Kip family (including p21/WAF1, p27/Kip1 and p57/Kip2). These molecules inhibit the functioning of CDK4/6-cyclin D and CDK 2-cyclin E (in the G_1/S phase) and CDK 2-cyclin A complexes (in the S-phase) thereby blocking the progression of the cell cycle from the G_1 to the S-phase. In cancer, the cells are unable to pause at both the checkpoints of the cell cycle (G_1/S and G_2/M) resulting in a deregulated cell proliferation (Fig. 2).

Cells encountering unfavorable growth patterns by default, enter the apoptotic pathway. A number of different proteases called caspases are involved in the apoptosis. Apoptosis either goes through the receptor mediated or extrinsic pathway utilizing caspase 8 and/or 10 or, the mitochondrial or intrinsic pathway, involving caspase 9. The expression of caspase 3 and 6 are critical for the progression into apoptosis. It is highly regulated by a set of proteins, for example Bcl-2 family of proteins and IAP proteins. Alterations in the Akt pathway are associated with the majority of cancers as it inhibits the catalytic activity of caspase 9 (Chandra and Kaufman, 2003).

It is important to understand these mechanisms of cancer in order to develop therapeutic measures for the treatment of neoplasms. The application of treatment strategies (surgery, radiation therapy, chemotherapy and biological therapy) has shown a cure of more than 50% in patients diagnosed with cancer. Of all the methods, chemoprevention is widely accepted to suppress or prevent carcinogenesis but treatment of cancers with individual chemotherapeutic agents has not increased the cure rates. The primary goal of combination chemotherapy is to improve the killing of multidrug resistant tumor cell lines and to slow down the development of drug resistance. This depends on the dose density, synergy between drugs and the sequence of administration of combination chemotherapy and timing of their administration (Shah and Schwartz, 2000). The success behind the use of two or more agents in combination chemotherapy is because they (a) act through different mechanisms (b) individually possess a cell killing ability (c) exhibit different levels of toxicity or block two or more points in the biochemical pathway (Gringauz, 1997).

PHYTOCHEMICALS AND CANCER

A number of phytochemicals have been demonstrated to possess antitumor effects in various experimental systems. They afford the opportunity to affect many different targets or portions of the signal transduction pathway that modulate gene expression, cell cycle progression, proliferation, cell mortality, metabolism and apoptosis. Several of the mechanisms mentioned above have been implicated in the action of the phytochemicals on various signal transduction pathways and they are listed in Table 2 as well as depicted in Figs 1 and 2.

TYPES OF HERB–DRUG INTERACTIONS

Many kinds of herb–drug interactions can pose serious health problems in patients. The interaction could be pharmacokinetic or pharmacodynamic in nature. Pharmacokinetic interactions result in altered absorption, distribution or elimination of the drug. The interactions can alter the gastrointestinal motility, compete for plasma binding, inhibit biotransformation and compete for renal tubular secretions. For example, the cytochrome P-450 isoenzyme system, the most common system of metabolism, can alter the availability of theophylline, caffeine etc., thereby leading to a decrease in the therapeutic response. Inhibitors of the cytochrome enzyme system should be avoided when using theophylline therapy.

In the traditional Indian system of medicine, piperine in 'Trikatu' is known to enhance the bioavailability of drugs such as theophylline (Bano *et al.*, 1991), oxyphenyl butazone (Mujumdar *et al.*, 1999) and rifampicin (Zutshi *et al.*, 1984). It has been demonstrated that 'Trikatu' interferes with the pharmacokinetic process in the case of phenyl butazone (Mujumdar *et al.*, 1999). Piperine inhibits the glucuronidation of EGCG (epigallocatechin gallate) in the small intestine as well as slowing the gastrointestinal transit. This increases its availability and residence time in the intestine allowing for greater absorption. The increase in the bioavailability of EGCG in plasma may improve its cancer preventive activity *in vivo* (Lambert *et al.*, 2004). Shoba *et al.* (1998) showed that coadministration of piperine and curcumin to humans and rats enhanced the bioavailability of curcumin by 2000% and 154%, respectively, due to an inhibition of the glucuronidation of curcumin as the phenolics are heavily metabolized in the form of glucoronide conjugates prior to reaching the plasma (Reddy *et al*., 2003).

Pharmacodynamic interactions cause alterations in the way a drug or natural medicine affects a tissue or organ system. These interactions affect drug action in a qualitative way, either through an enhancing effect (synergistic or additive actions) or an antagonizing effect. The combinations are considered to be synergistic if the effectiveness is greater than the effect of either the agent alone or the sum of the effects of the individual agents and antagonism is less than the expected effect of the combination (De Vita *et al.*, 1975). Combination treatment with genistein (isoflavone from soy) and β-lapachone (a simple plant product) probably involves different mechanisms of action in inducing apoptosis in human prostate adenocarcinoma PC3 cells. Caspase-3 is the main target in genistein-induced apoptosis and NAD(P)H: quinone oxidoreductase (NQO1) in β-lapachone induced apoptosis in PC3. Experimental data demonstrated that NQO1 is the main target in β-lapachone-genistein combination induced apoptosis and is more efficacious in combination than single drug treatment (Kumi-Diaka *et al.*, 2004).

Interactions that occur at the same receptor site are usually inhibitory, whereas interactions involving different receptor sites may either inhibit or potentiate the process. 5-Fluorouracil inhibits thymidylate synthase in the presence of 5,10-methylenetetrahydrofolate. Leucovorin and 5-fluorouracil act on the same target but the former increases the 5,10-methylenetetrahydrofolate concentrations thereby enhancing the cytoxicity of the latter exhibiting synergy (Grem *et al.*, 1987; Grem *et al.*, 1992).

IDENTIFICATION OF DRUG INTERACTIONS

The identification of synergistic combinations and their optimal dose ratio is based on trial and error. A variety of methods are used to study the interaction of drugs in combination, and for the same set of data, the methods can give discordant results. The coexistence of several methods also does not mean that they are equally valid. Different methodologies namely the isobologram method (Loewe, 1953), the fractional product method of Webb (1963) and the combination index method of Chou and Talalay (1984) are generally used to determine drug–drug interactions.

Most studies have utilized quantitative methods to detect alterations in cell cycle and proliferation, and apoptosis of the cells. These studies are based on the expression of genes such as NF-κB, Ap-1 and other apoptotic genes; the activity of caspases; DNA fragmentation and cytochrome C analysis (Mertens-Talcott and Percival, 2005; Tanos *et al.*, 2002; Seeram *et al.*, 2005; Ohishi *et al.*, 2002).

HERBAL EXTRACTS AND DRUG INTERACTIONS

Drug interactions can cause clinical problems. For example, some herbal medicines may contain inorganic contaminants such as arsenic, lead, mercury or intentionally added pharmaceuticals, which can increase the potential for adverse drug interactions. Most of the herbs contain active constituents that produce side effects such as cardiotoxicity, hepatotoxicity, may produce carcinogenic metabolites or alter the metabolism. For example, the tea made from the herb *Larrea tridentate* is not recommended for the above said reasons. St John's Wort, a widely used herbal product, has been found to be metabolized by cytochrome P450 by increasing the CYP3A4 activity (Roby *et al.*, 2000).

Most of the herbal formulations are known to enhance the cytotoxic effect of drugs through unknown mechanisms. Calcium channel blockers have been found to increase the toxicity of synthetic anticancer drugs such as paclitaxel (Racker *et al.*, 1986). Herbs like *Angelica sinensis* or *Zingiber officinale* might increase the

Table 1. Interactions of various synthetic drugs with natural products

S. No	Natural products	Synthetic drugs/natural products	Activity	System studied	References
1	Quercetin	Carboxytriazole	Synergism	Human breast carcinoma cells	Yeh *et al.*, 1995
2		Tamoxifen		Human melanoma cells	Piantelli *et al.*, 1995
3		Adriamycin		Human breast-cancer cell line	Scambia *et al.*, 1994
4		Triazofurin		Human ovarian carcinoma cells	Shen *et al.*, 1999
5		*cis*-Diamminedichloroplatinum(II) (CDDP)			
6		Cytosine arabinoside (Ara-C)		HL-60 cells Human leukemic cells	Teofili *et al.*, 1992
7		Reseveratol	Additive Additive Synergistic	Human pancreatic carcinoma cells Squamous carcinoma cells Human leukemia cells	Mouria *et al.*, 2002 Elattar and Virji, 1999 Mertens-Talcott and Percival, 2005
8	Tea Catechins epigallocatechin gallate	Sulindac	Synergism Synergism	Human lung carcinoma cells Min mice Levels of gene expression in human lung carcinoma cells	Suganuma *et al.*, 1999 Fugiki *et al.*, 2003
9		(-)-Epicatechin		Human lung carcinoma cells BALB/c-3T3 cells	Suganuma *et al.*, 1999
10		Tamoxifen		Human lung carcinoma cells	Suganuma *et al.*, 1999
11		Epigallocatechin Epicatechin gallate Epicatechin		Min mice HepG2 cells	Fugiki *et al.*, 2003 Williams *et al.*, 2003
12		Curcumin	Synergism		Khafif *et al.*, 1998
13	Thearubigins	Genistein	Synergism	Human prostate tumor cell	Sakamoto, 2000
14	Catechin	NS398	Synergism	Bladder and prostate cancer cells	Farivar-Mohseni *et al.*, 2004
15	Genistein	Eicosapentanoic acid	Synergism	Human breast carcinoma cells	Nakagawa *et al.*, 2000
16		Tamoxifen		Dysplastic and cancerous breast cells	Tanos *et al.*, 2002
17		5-Fluorouracil		Colon cancer cells	Hwang *et al.*, 2005
18	Curcumin	Doxorubicin	Synergism	Hepatocellular carcinoma cells	Notarbartolo *et al.*, 2005
19		Cisplatin	Synergism	Ovarian carcinoma cells	Chan *et al.*, 2003
20		Genistein	Synergism	Breast cancer cells	Wolff *et al.*, 1993
21		Vinorelbine	Synergism	H520 cells	Sen *et al.*, 2005

Table 2. Mechanism of action of phytochemicals against cancer

S. No	Mechanisms of action	Phytochemicals	References
1	Inhibition of the activation of NF-κB	Curcumin[a] Capasaicin[a] Resveratrol[a] Sanguinarine[a] Emodin[a] Flavopiridol	Singh and Aggarwal, 1995 Singh *et al.*, 1996 Estrov *et al.*, 2003 Chaturvedi *et al.*, 1997 Kumar *et al.*, 1998 Takada and Aggarwal, 2004
2	Inhibition of the AP-1 activation pathway	Curcumin[a] Capsaicin[a] Resveratrol[a] Green tea catechins[a] 6-gingerol[a]	Dorai and Aggarwal, 2004
3	Inhibition of the tyrosine kinase activity of EGFR	Curcumin[a] EGCG[a] Genistein[a] Resveratrol[a]	Korutla *et al.*, 1995; Sachinidis *et al.*, 2000
4	Inhibition of the RTK related pathways of signal transduction		Wang *et al.*, 2004; Korutla *et al.*, 1995; Adhami *et al.*, 2004
5	Inhibition of the multidrug resistance related proteins	Curcumin EGCG	Anuchapreeda *et al.*, 2002 Hong *et al.*, 2003
6	Blocking of the phosphatidyl inositol-3 kinase signaling pathway		Reddy and Aggarwal, 1994 Leu *et al.*, 2003
7	Blocking of the cell cycle at various phases	Curcumin[b] Resveratrol[b] EGCG[b]	Mukhopadhyay *et al.*, 2002 Estrov *et al.*, 2003 Gupta *et al.*, 2003
8	Inhibition of the induction of COX-2	Reseveratol Curcumin Genistein, Catechin	Dong, 2003 Plummer *et al.*, 1999; Dorai and Aggarwal, 2004

[a] Molecular targets depicted in Fig. 1.
[b] Inhibitors of cell cycle shown in Fig. 2.

toxicity of anticancer drugs because they are rich in calcium chain blockers (Poppenga, 2002).

The focus of the current review is to investigate the synergistic interactions within the dietetic phytochemicals such as quercetin, tea catechins, curcumin genistein, resveratrol and between phytochemicals and conventional synthetic drugs in the treatment of cancer. Interactions of various synthetic drugs with natural products from different herbs on specific targets are listed in Table 1.

DIETETIC PHYTOCHEMICALS AND DRUG INTERACTIONS

Quercetin

Quercetin (3,3′,4′,5,7-pentahydroxyflavone) is a flavonoid that serves as the backbone for many other flavonoids. It exhibits the highest activity when compared with other flavonoids, and many medicinal plants owe much of their activity to their high quercetin content (Havsteen, 1983).

Carcinogenesis is a multistep process and oxidative damage leads to the formation of tumors through several mechanisms. Polyphenols such as ellagic acid, quercetin, resveratrol and ellagitannins exhibit antioxidant, antiinflammatory and antiproliferative activities. The polyphenols present in vegetables and fruits regulate cell proliferation and induce apoptosis (Sun *et al.*, 2002; Chu *et al.*, 2002). Mouria *et al.* (2002) demonstrated that resveratrol and quercetin additively activate the caspase 3 in human pancreatic carcinoma cells and activate growth and DNA synthesis in squamous carcinoma cells (Elattar and Virji, 1999) while Mertens-Talcott and Percival (2005) found that in combination they synergistically induce apoptosis in human leukemia cells. It is believed that these compounds interact with different signal transduction pathways or stabilize each other. Igura *et al.* (2001) found that this combination inhibits aspects of angiogenesis such as proliferation, migration and tube formation of endothelial cells.

Quercetin has been shown to reduce cell proliferation, cause cell cycle arrest in the G_0/G_1 phase (Yoshida *et al.*, 1990), the G_2/M phase (Choi *et al.*, 2001), at the G_1 and S phase boundary (Yoshida *et al.*, 1990) and induce caspase-3 activity and apoptosis (Wang *et al.*, 1999) in *in vitro* experiments with various cell lines. It is also found to inhibit the 1-phosphatidylinositol kinase (PI) activity therefore leading to a decrease in the inositol 1,4,5-triphosphate (IP_3) concentration (Weber *et al.*, 1997) (Fig. 1). The PI to 1-phosphatidyl inositol 4- phosphate (PIP) signal transduction pathway, which is elevated in human cancer cells (Singhal *et al.*, 1994),

is an attractive target for preventing cancer. Therefore compounds that inhibit PI signal transduction activities should be good candidates.

Quercetin has been found to act synergistically with triazofurin in human ovarian carcinoma cells [OVCAR-5] (Shen *et al.*, 1999). Triazofurin therapy leads to the reduction of cellular GTP pool and decreased IP_3 concentration (Weber *et al.*, 1997). The latter is brought about by blocking the S phase of the cell cycle (Jayaram *et al.*, 1982). Since triazofurin and quercetin block different biochemical targets and arrest different phases of cell cycle, the combined therapy yields a synergistic reduction of IP_3 concentration by 30% (Shen *et al.*, 1999). Also it is possible to use lower concentrations of triazofurin during combination therapy thereby decreasing the side effects.

Yeh *et al.* (1995) proved that quercetin could enhance the action of carboxytriazole in human breast carcinoma MDA-MB-435 cells. Quercetin depresses IP_3 levels that eventually decrease the cytosolic calcium concentration while carboxytriazole inhibits calcium influx into cells. Quercetin is found to enhance the antiproliferative activity of *cis*-diamminedichloroplatinum(II) (CDDP) and busulfan (Scambia *et al.*, 1993). Quercetin significantly synergized the inhibitory activity of cytosine arabinoside (AraC) on HL-60 cell growth. Quercetin from 10 nm to 10 μm and AraC from 0.01 nm to 10 μm concentration inhibited the colony formation in human leukemic cells (CFU-L) suggesting that this combination can be used in the treatment of acute leukemias (Teofili *et al.*, 1992).

Tea catechins

Green tea is associated with a decreased incidence of cancer. It contains the catechins epigallocatechin gallate (EGCG), epigallocatechin (EGC), epicatechin gallate (ECG) and epicatechin (EC). EGCG is believed to be the active constituent in green tea in terms of its chemopreventive potential (Komori *et al.*, 1993).

Sulindac is a non steroidal antiinflammatory drug that is used as a cancer preventive agent, but the usage of this is restricted due to its adverse side effects. High doses of this drug inhibit COX-1, which can lead to gastrointestinal bleeding. The apoptotic inducing activity of EGCG on lung cancer PC-9 cells has been found to be synergistically enhanced by other chemopreventive agents such as sulindac and tamoxifen (Suganuma *et al.*, 1999). Suganuma *et al.* (2001) reported that the antitumor effects of EGCG were synergistically increased by sulindac and the tumor incidence decreased in mice with multiple intestinal neoplasia and apoptosis induced against colon carcinogenesis of rats making it a suitable candidate in combination with NSAIDs (Ohishi *et al.*, 2002). Since EGCG also inhibits COX, it may be expected that both EGCG and sulindac inhibit tumor by strongly blocking the enzyme activity.

Black tea contains catechins, which are oxidized to the pigments theaflavins and thearubigins. Thearubigins are the most abundant constituent of black tea but very little information is available about the role of polyphenols in black tea in cancer prevention. Sakamoto (2000) examined the effect of two flavones thearubigins (from black tea) and genistein (from soybean) on human prostate tumor cell growth and found that though low concentrations of thearubigins alone did not inhibit the growth of tumor cells, when combined with genistein it suppressed the growth indicating synergy between the two natural products. Cell growth inhibition was proportionally accompanied by cell cycle perturbation at the G2/M phase. Green tea compounds have been shown not only to enhance doxorubicin transport into malignant cells but also to protect the myocardium against its cardiotoxic effects (Sugiyama and Sadzuka, 2004).

Curcumin

Curcumin (diferulolyl methane) extracted from the rhizomes of *Curcuma* species has antiinflammatory, antitumor and antioxidant properties (Plummer *et al.*, 1999; Ammon and Wahl, 1991). Curcumin has more than one defined mechanism of action namely, either by blocking the initiation of carcinogenesis or by suppressing the malignant expression of initiated cells (De Flora, 1998). It has been found to suppress many transcription factors such as TNF-α and NF-κB (Aggarwal *et al.*, 2003; Singh and Aggarwal, 1995). NF-κB activation (interference of NF-κB signaling) is required for the cytotoxicity of doxorubicin and its analogs, therefore curcumin may possibly increase its (doxorubicin) tumor cell response by blocking NF-κB activation (Ashikawa *et al.*, 2004; Somasundaram *et al.*, 2004). Notarbartolo *et al.* (2005) studied the effects of curcumin alone and in combination with conventional anticancer drugs such as cisplatin and doxorubicin on the hepatocellular carcinoma cell line. Although curcumin strongly inhibited NF-κB activation, its effects in combination with doxorubicin were additive and subadditive but not synergistic. At the level of gene expression there was a down-regulation of NF-κB target genes such as *COX-2*, *Bcl-X_L* and *c-myc* when curcumin was combined with cisplatin. In addition, curcumin potentiated the antitumor and apoptotic effects of cisplatin in ovarian carcinoma (Chan *et al.*, 2003).

Many pesticides increase the risk of breast cancer in women (Wolff *et al.*, 1993). It is possible that the pesticide induced growth of MCF-7 cells can be inhibited by blocking the activities of protein kinases or by blocking the estrogen-dependent signaling pathway (Verma *et al.*, 1997; Chaudhary and Aviolli, 1996). Curcumin and genistein showed a synergistic inhibitory effect against the proliferation of 17 beta-estradiol induced growth of MCF-7 (Soto *et al.*, 1995). The development of dietetic (curcumin and genistein from turmeric and soybean, respectively) preventive strategies can be recommended for the treatment of such hormone related cancers and to reduce the carcinogenic effects of estrogenic pesticides.

Vinorelbine, a semi-synthetic vinca alkaloid is an effective and less toxic chemotherapeutic agent (Bunn, 2002). Pretreatment with curcumin enhances the apoptotic effect of vinorelbine (by the mitochondrial pathway in H520 cells) by downregulating anti-apoptotic Bcl-2 and Bcl-X_L, upregulating pro-apoptotic Bcl-xs and Bax and, activating caspase-9 and -3. The suppression of NF-κB and Ap-1 by both curcumin and vinorelbine may possibly explain their combined antiproliferative

and apoptotic effects (Sen *et al.*, 2005). The identification of curcumin having potential synergy with standard cytotoxic drugs can lead to low therapeutic doses of the drugs thereby reducing their toxicity and long-term side effects.

Genistein

Genistein, a soy derived phytoestrogen belonging to the 'isoflavone' family has potential as a chemotherapeutic agent capable of inducing apoptosis by inhibiting DNA topoisomerase, inhibiting angiogenesis (Sarkar and Li, 2003; Ye *et al.*, 2004; Nakagawa *et al.*, 2000) or suppressing tumor promoting proteins such as COX-2 (Ye *et al.*, 2004). Nakagawa *et al.* (2000) demonstrated *in vitro* that genistein acts synergistically with eicosapentanoic acid altering the glucose oxidation thereby inhibiting the proliferation of human breast carcinoma cells.

Chemoresistance involves the expression of survival genes such as Glut-1, tumor suppressor genes such as p53 (Gregg and Semenza, 2004; Airley *et al.*, 2001) or ATP binding cassette-containing family of proteins like P-glycoproteins (Schinkel and Jonker, 2003). 5-Fluorouracil (5-FU) is one of the widely used chemotherapeutic drugs targeting various cancers but its chemoresistance remains a major obstacle in clinical settings. Natural products have also been seen to overcome drug resistance in a few of these cell lines. Hwang *et al.* (2005) focused on the combined cytotoxicity of 5-FU and genistein on HT-29 colon cancer cells and observed that the combination resulted in a reduction of the survival signal Glut-1 and an elevation of pro-apoptotic p53 and p21. The combination also abolished the up-regulated state of COX-2 and prostaglandin secretion caused due to only 5-FU treatment.

A significant synergistic inhibitory effect was noted with the combination of genistein and tamoxifen on the growth rate of dysplastic and an additive anti-proliferative effect on cancerous breast cells. This can be of significant medical application in treating mammalian dysphasia, since currently there is no other chemopreventive treatment available. It can also be an effective adjuvant therapy in women with breast cancer (Tanos *et al.*, 2002).

SEMISYNTHETIC ANTICANCER AGENTS

Natural products have the potential to provide the pharmacologist with a source of novel structures, on the basis of which most of the current cancer drugs have been synthesized. Many novel chemotypes such as taxanes, vinca alkaloids, podophyllotoxins and camptothecins show a range of cytotoxic activities and act as antitumor agents.

Paclitaxel (Taxol®) is a chemotype from the active principle of pacific Yew tree, *Taxus brevifolia*, which stabilizes microtubules, promotes tubulin assembly and inhibits cell proliferation. It is used in the treatment of lung, ovarian, breast cancer and Kaposi's sarcoma (Shu, 1998). There are many possibilities for drug–drug interactions to occur with the taxanes. Many studies have investigated the different combinations of taxanes with other cytotoxic agents. Triazofurin and Taxol which targeted different sites in the mitotic spindle formation are synergistically cytotoxic in human ovarian, pancreatic, lung and breast carcinoma cells (Taniki *et al.*, 1993). Also gallium nitrate, a ribonucleotide reductase inhibitor, exhibits synergism with Taxol (Hata *et al.*, 1994).

Modulation of multidrug resistance (MDR) proteins such as P-glycoprotein facilitates oral drug uptake and is an example of a beneficial drug–drug pharmacokinetic interaction. Drugs that inhibit P-glycoprotein such as cyclosporin increase the oral bioavailability of paclitaxel to achieve therapeutically relevant drug concentrations in plasma (Bardelmeijer *et al.*, 2000; Kruijtzer *et al.*, 2002). Phase II clinical studies have shown that combination of cyclosporin and paclitaxel are clinically effective in lung and stomach cancer (Kruijtzer *et al.*, 2002).

Doxorubicin is not a good choice of drug in the treatment of patients due to the risk of drug resistance and its cardiotoxicity (Dierás *et al.*, 1997). Docetaxel (a semisynthetic compound, prepared from non-cytotoxic precursor, 10-deacyl baccatin III from Yew tree *Taxus baccata*) can be combined with doxorubicin or vinca alkaloids (isolated from *Catharanthus roseus*) such as vinorelbine to provide high response rates and acceptable toxicity. Baker and Dorr (2001) have reviewed in detail the interactions of taxanes with a number of other cytotoxic drugs. Etoposide (4′-dimethylepipodophyllotoxin-9-4, 6-O-ethylidene-β-D-glucopyranoside) a modified analog of podophyllotoxin (from *Podophyllum peltatum*) is an antineoplastic agent, which inhibits topoisomerase II and has been also found to act in synergism with gemcitabine (van Moorsel *et al.*, 1999).

CONCLUSION

This review has presented examples of a very important concept, namely that of drug–drug interaction involving natural products and synthetic drugs that are typically prescribed for cancer patients. These patients are particularly at high risk from drug–drug interactions, because the treatment commonly involves multiple medications, including cytotoxic chemotherapy, hormonal agents and supportive care drugs. In addition, it is estimated that 50% of oncology patients use alternative and herbal medicines, often without their doctors' knowledge. Hence the present review is apt. The above studies provide evidence that various combinations of natural products and drugs can work in many ways.

1. Targeting multiple sites in the biosynthetic pathways. Most of the phytochemicals such as EGCG, resveratrol, genistein and curcumin block the transcription factors AP-1 and NF-κB (Fig. 1) which normally enhance cell proliferation and cell survival by targeting multiple sites of the pathway.
2. Different mechanisms of action. Cyclosporin has found to increase the bioavailability of paclitaxel by maintaining the expression of P-glycoproteins.
3. Blocking the functioning and maintenance of some essential macromolecules. Certain phytochemicals such as curcumin have been found to possess inhibitory activities against topoisomerase enzymes which

are required for the normal survival of the cell. Blocking this along with inhibiting other pathways can readily increase the efficacy of the drug.

The potential to interact is difficult to predict hence requires, a deep knowledge of the products, its detailed chemical composition, information on the dose and level of exposure, and details of the mechanism of action as well as the target site. Although results from *in vitro* experiments cannot be directly extrapolated to clinical effects but such studies help in elucidating the various pathways involved in the overall disease process. Integration of modern medicine with traditional knowledge, robust use of science and technologies with a systems biology approach could open up new opportunities for immunodrugs and combination therapy.

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