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ORIGINAL PAPER

Natural products and their role in cancer therapy

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Abstract This paper documented several natural products that have antineoplastic activities. Detailed descriptions of the mechanism of action of these products are given. Side effects of these natural products are also described. Based on these side effect profiles and their benefits, these natural products could be used as adjuvant cancer therapies. Traditional anticancer agents usually have debilitating side effects. These natural products would be of great benefit due to their anticancer activities. Additionally, some of these natural products can work proactively in preventing cancer formation with their chemopreventive properties. Incorporation into diet can be recommended after discussion with physician and other health care professionals.

Keywords *Bupleuri radix* · *Curcuma longa* · Green tea catechins · Panax ginseng · *Phyllanthus urinaria* · *Polygonum cuspidatum*

Abbreviations

ACAT	A-cholesterol acyltransferase
AE-BS	*B. scorzonerifolium* extracted with acetone
CDDP	cis-diamminedichloroplatinum(II)
CDK	Cyclin-dependent kinase
CLU	Clusterin
CYP	Cytochrome P_{450}
dD AVP	Vasopressin derivative
EC	(-)-Epicatechin
ECCs	Esophageal cancer cells
ECG	(-)-Epicatechin-3-gallate
EGC	(-)-Epigallocatechin
EGCG	(-)-Epigallocatechin-3-gallate
GADD153	Growth arrest and DNA damage-inducible gene 153
IGF-1	Insulin-like growth factor I
LLC	Lewis lung carcinoma
MAPK	Mitogen-activated protein kinase
NF-kappaB	Nuclear factor kappa B
NK	Natural killer
PCWE	*Polygonum cuspidatum* water extract
Rh2	Ginsenoside Rh2
TPA	12-O-Tetradecanoyl phorbol-13-acetate
VEGF	Vascular endothelial growth factor
XIAP	X-linked inhibitor of apoptosis

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Introduction

Interest in the use of natural products has grown dramatically in the Western world. Recent estimates suggest an overall prevalence for herbal preparation use of 13–63% among patients with cancer [1]. Upon careful consultation with a physician, natural products can be used as an anticancer therapy. The side effects of natural products are listed in this paper (Table 1). Different plants and isolated compounds are selected for this paper. Some have anticancer activities. Others have chemopreventive effect. Antineoplastic activities of these natural products are achieved through various mechanisms [2]. Various natural products and their mechanism of action (Table 2) are documented in this paper.

Coptidis Rhizoma

Coptidis rhizome is a plant that has been used as traditional herb medicine in the Eastern Asia [3]. Previous studies

Table 1 Various IC (50) values and side effects for different natural products

Plant	Cell type	IC_{50}	Side effects	References
Green tea catechins	PNT1A cell line	83.6 ± 1.3 μg/ml	Studies have shown reduced cell growth and DNA damage of normal cells	[38–41]
	PC-3 cell line	202.3 ± 3.2 μg/ml	Insomnia	
Panax ginseng	Ovarian cancer cell line	40 ± 5 μM	Low	[22–24]
			Interaction with other drugs	
Polygonum cuspidatum	LLC cells	6.8 μmol/l	Not to be used during pregnancy	[6, 13–16]
			Large dosage or long term use can be toxic to kidneys	
Bupleuri radix	A549 human lung cancer cells	59 ± 4.5 μg/ml	Mildly toxic	[6, 22, 23]
			Overdose can cause headaches, dizziness, vomiting, tremors, gastroenteritis, and pathogenic erections	
			There were reports of cases of mortality of broncho-interstitial pneumonia suspected were being caused by the combined use of Bupleuri Radix and interferon	
			Large dosages or long-term usage can lead to kidney toxicity	
Phyllanthus urinaria	Lewis lung carcinoma cells	2 mg/ml	No side effects on normal cells	[11, 20]
Curcuma longa	A549 cell line	50 μM	Reported side effects are uncommon and are generally limited to mild stomach distress	[30–37]
	H1299 cell line	40 μM	There is some evidence that turmeric extracts can be toxic to the liver when taken in high doses or for a prolonged period of time	
			There is a possibility of allergic contact dermatitis from turmeric	
			It should be avoided during pregnancy	
Adlay seed	Lung tumor	30% powder	Not known	[20]
Ellipticine	V79 cell lines	Ranging from 0.25 to 0.40 μM	A number of toxic side effects including nephrotoxicity	[7–11]
Red grape wine	He La cell lysates	10 μM	Deficiencies in Vitamin B1, B3 (Niacin), NAD, Acetyl Coenzyme A, B5, P5P (Pyridoxal–5-Phosphate) induced by acetaldehyde	[10]
Hemsleya amabilis	Human astrocytoma U87 cells	25 μg/ml	Low	[24]
	Breast cancer cells MDA-MB-231and	50 μg/ml		
Coptidis rhizoma	YES-1	2.2 μg/ml	Allergic reaction, allergic rash, dizziness, headache, tinnitus, nausea, vomiting, palpitation, shortness of breath, abdominal fullness, diarrhea and reduction in red blood cells	[3–6]
	YES-2	3.0 μg/ml		
	YES-3	0.25 μg/ml		
	YES-4	2.8 μg/ml		
	YES-5	2.5 μg/ml		
	YES-6	0.5 μg/ml		
Embelin	PC-3	3.7 μM	Large doses can lead to kidney toxicity	[6 17, 18]
	LNCaP	5.7 μM		
α-tomatine	Liver carcinoma cells	~0.5 μg/ml	Not known	[25–29]

demonstrated that the herbal medicine, Oren-to, had anti-tumor effects on esophageal cancer cells (ECCs) in vitro. MTT assay showed that, of the seven constituents, only the aqueous extract of *C. Rhizoma* had potent inhibitory effect on the proliferation of two types of ECC lines: YES-3 and YES-4. In addition, the proliferation of all six types of ECC lines (YES-1 to YES-6) was inhibited in a dose-dependent manner, when cocultured at each concentration of *C. Rhizoma* for 72 h [3].

Mechanism

The effect of berberine, a major component with antifungal properties contained in *C. Rhizoma*, on the lymph node

Table 2 Various mechanism of action for different natural products

Plant	Mechanism	References
Green tea catechins	Inhibit angiogenesis through blocking the induction of VEGF	[40, 41]
	Inhibit Erk-1 and Erk-2 activation in a dose-dependent manner	
Panax ginseng	Arrest the cell cycle of melanoma cells	[21]
Polygonum cuspidatum	Induce S-phase arrest and apoptosis	[6, 13–16]
Bupleuri radix	Inhibit telomerase activity and induce apoptosis	[22]
Phyllanthus urinaria	Induce apoptosis by the down-regulation of Bcl-2 gene expression	[19, 20]
Curcuma longa	Inhibit lipooxygenase activity and is a specific inhibitor of cyclooxygenase-2 expression	[30, 33–35]
	Inhibit the initiation of carcinogenesis by inhibiting the cytochrome P-450 enzyme activity and increasing the levels of glutathione-S-transferase	
	Phosphorylation and activation of c-jun N-terminal kinase and p38 MAPK as well as inhibition of constitutive NF-kappaB transcriptional activity inducing apoptosis	
	Inhibit the enzymatic activities of cholinesterase systems	
Adlay seed	Inhibit basal and TPA-induced COX-2 expression in a dose-dependent fashion	[20]
Ellipticine	DNA intercalation and/or inhibition of topoisomerase II	[8, 9]
	Formation of CYP-mediated covalent DNA adducts	
Red grape wine	Inhibition of calcium and calmodulin-promoted phosphodiesterase activity	[8]
	Metabolize to piceatannol that has antileukemic activity and is a tyrosine kinase inhibitor	
	Exert its growth-inhibitory/apoptotic effect by activating the de novo ceramide synthesis pathway	
Hemsleya amabilis	Interfere with the interaction of tumor cells with extracellular matrix, or signals of the interaction	[5]
Coptidis rhizoma	Anti-activator protein-1 transcriptional activity cause the repression of expression of urokinase-type plasminogen activator	[4]
Embelin	Inhibit the X-linked inhibitor of apoptosis (XIAP)	[18]
α-tomatine	Suppression of IGF-stimulated cell cycle progression	[26–28]
	Inhibit cell cycle progression via reduction in the cyclin D level and retention of p27 in cyclin E–cdk2, thus leading to inhibition of G(1) CDK activities	

metastasis of murine lung cancer was examined. Oral administration of berberine for 14 days significantly inhibited the spontaneous mediastinal lymph node metastasis produced by orthotopic implantation of Lewis lung carcinoma (LLC) into the lung parenchyma in a dose-dependent manner but did not affect the tumor growth at the implantation site of the lung. Anti-activator protein-1 transcriptional activity of non-cytotoxic concentrations of berberine caused the inhibition of the invasiveness of LLC cells via the repression of expression of urokinase-type plasminogen activator [4, 5].

IC_{50}

The antiproliferative activity of *C. Rhizoma* and the major component berberine was investigated in eight human pancreatic cancer cell lines. A tetrazolium dye (MTT) assay was used to determine IC_{50} values, i.e., the concentration required to inhibit proliferation of cancer cells by 50%, after the eight cell lines were exposed to the two agents for 72 h. The IC (50) value for berberine was correlated positively with that for *C. rhizoma*. *C. rhizoma* killed tumor cells more effectively than purified berberine when normalized to the level of berberine present in the herb. From the oligonucleotide array data, we selected 20 and 13 genes with strong correlations with IC_{50} values for berberine and *C. rhizoma*, respectively. Among these 33 genes, the levels of expression of 12 were correlated with the IC_{50} values of both agents, suggesting that these genes are associated with tumor-killing activity of berberine in *C. rhizoma*. Expression of the remaining 21 genes was correlated with the IC (50) value of either purified berberine or *C. rhizoma* [6].

The IC_{50} of *C. Rhizoma* for YES-1 to YES-6 was 2.2, 3.0, 0.25, 2.8, 2.5, and 0.5 μg/ml, respectively, berberine showed potent antitumor effects on all six types of ECC lines as well as *C. Rhizoma*. In addition, the IC_{50} of berberine exhibited a positive correlation with that of *C. Rhizoma* in six types of ECC lines examined. Cell cycle analysis of *C. Rhizoma*-treated cancer cells showed the accumulation of cells in the G0/G1 phase and relative decrease of the S-phase. These results support the

possibility that the use of *C. Rhizoma* containing abundant berberine may be useful as one of alternative therapies for esophageal cancers [3].

Side effect

Coptidis Rhizoma is relatively safe but could be associated with the following side effects: allergic reaction, allergic rash, dizziness, headache, tinnitus, nausea, vomiting, palpitation, shortness of breath, abdominal fullness, diarrhea, and reduction in red blood cells [7].

Polygonum cuspidatum

Resveratrol, a polyphenol present in the root of a plant called *P. cuspidatum*, exhibits a wide range of biological and pharmacological activities both in vitro and in vivo. Its content was much higher in *P. cuspidatum* than in grape [8]. It has been shown to exert a potent chemopreventive effect in carcinogenesis models and to induce cell growth inhibition and apoptosis in human tumor cells, including melanoma cells. Malignant melanoma is considered to be a chemotherapy-refractory tumor, and the commonly used anticancer drugs do not seem to modify the prognosis of metastatic disease. To further evaluate the therapeutic potential of resveratrol in the treatment of melanoma, three human melanoma cell lines with different levels of resistance to temozolomide, an antitumor triazene compound, were selected. The cell lines were subjected to resveratrol treatment and analyzed for cell growth inhibition, cell cycle perturbation, and apoptosis induction. Resveratrol markedly impaired proliferation of both the temozolomide-sensitive M14 and the temozolomide-resistant SK-Mel-28 and PR-Mel cell lines. The latter cell line was twofold more resistant to the drug than M14 and SK-Mel-28 cells. The sensitivity of normal human keratinocytes to resveratrol was found to be significantly higher than that of M14 and SK-Mel-28 cells and similar to that of the PR-Mel cell line. This suggests a possible good in vivo therapeutic index for resveratrol [9].

Mechanism

Studies show that the growth-inhibitory effect of resveratrol on melanoma cells is mostly due to its ability to induce S-phase arrest and apoptosis [9]. The pharmacological effects of *P. cuspidatum* water extract (PCWE) on lipid biosynthesis were investigated in cultured human liver cancer cells (HepG2). The addition of PCWE (5 and 20 μg/ml), which had no effect on cell proliferation and cellular protein content, caused a marked decrease in the cellular cholesterol content, particularly, the cholesteryl ester content following 24 h of incubation. The incorporation of (14)C-oleate into the cellular cholesteryl ester fraction was also decreased remarkably during incubation for 6 and 24 h. The effect of PCWE on acyl-coenzyme A-cholesterol acyltransferase (ACAT) activity was studied in vitro to explore the mechanism by which PCWE inhibits cholesterol ester formation. It showed that PCWE, in a dose-dependent manner, remarkably inhibits ACAT activity. Among the main active chemicals of *P. cuspidatum*, resveratrol, a kind of flavonoid, decreased ACAT activity in a dose-dependent manner from the level of 10(-3) M. Theses results imply that PCWE reduces the cholesteryl ester formation in human hepatocytes by inhibiting ACAT [8].

IC_{50}

Resveratrol, at doses of 2.5 and 10 mg/kg, significantly reduced the tumor volume (42%), tumor weight (44%), and metastasis to the lung (56%) in mice bearing highly metastatic LLC tumors, but not at a dose of 0.6 mg/kg. Resveratrol did not change the number of CD4(+), CD8(+) and natural killer (NK)1.1.(+) T cells in the spleen. Therefore, the inhibitory effects of resveratrol on tumor growth and lung metastasis could not be explained by natural killer or cytotoxic T-lymphocyte activation. In addition, resveratrol inhibited DNA synthesis most strongly in LLC cells; its 50% inhibitory concentration (IC_{50}) was 6.8 μmol/l. Resveratrol at 100 μmol/l increased apoptosis to 20.6 ± 1.35% from 12.1 ± 0.36% in LLC cells and decreased the S-phase population to 22.1 ± 1.03% and 29.2 ± 0.27% from 35.2 ± 1.72% at concentrations of 50 and 100 μmol/l, respectively. Resveratrol inhibited tumor-induced neovascularization at doses of 2.5 and 10 mg/kg in an in vivo model. Moreover, resveratrol significantly inhibited the formation of capillary-like tube formation from human umbilical vein endothelial cells at concentrations of 10–100 μmol/l; the degree of the inhibition of capillary-like tube formation by resveratrol was 45.5% at 10 μmol/l, 50.2% at 50 μmol/l, and 52.6% at 100 μmol/l. Resveratrol inhibited the binding of vascular endothelial growth factor (VEGF) to human umbilical vein endothelial cells at concentrations of 10–100 μmol/l, but not at concentrations of 1 and 5 μmol/l. The degree of inhibition of VEGF binding to human umbilical vein endothelial cells by resveratrol was 16.9% at 10 μmol/l, 53.2% at 50 μmol/l and 47.8% at 100 μmol/l. The antitumor and antimetastatic activities of resveratrol might be due to the inhibition of DNA synthesis in LLC cells and the inhibition of LLC-induced neovascularization and tube formation (angiogenesis) of human umbilical vein endothelial cells by resveratrol [10]. When resveratrol was administered at a dose of approximately 25 mg, the plasma concentration of the free form ranged from 1 to 5 ng/ml;

administration of higher doses (up to 5 g) led to values of free resveratrol of up to 530 ng/ml.

Side effect

Polygonum cuspidatum should not be used during pregnancy. Overdose could be toxic to kidneys [7, 11].

Phyllanthus urinaria

Conventional solvent fractionation and bioactivity-based target assays were used to identify a new anti-cancer molecule from *P. urinaria*, a herbal medicinal plant used in South India. At each step of the purification process, the different fractions that were isolated were tested for specific antiproliferative activity. The pure compound and the crude ethyl acetate fraction that showed antiproliferative activities were evaluated for ability to target specific markers of apoptosis like bcl2, c-myc, and caspases and for effects on telomerase. Four specific cancer cell lines HEp2, EL-1 monocytes, HeLa, and MCP7 were used in this study. The results indicate that 7′-hydroxy-3′,4′,5,9,9′-pentamethoxy-3,4-methylene dioxy lignan was able to inhibit telomerase activity and also could inhibit bcl2 and activate caspase 3 and caspase 8 whose significance in the induction of apoptosis is well known [12].

Mechanism

The water extract of *P. urinaria* induced the apoptosis of HL-60 cells as demonstrated by morphological change, DNA fragmentation, and increased caspase-3 activity. However, normal human peripheral mononuclear cells remained viable under the same treatment. The *P. urinaria*-induced apoptosis of HL-60 cells was associated with the increased Bax gene expression and decreased Bcl-2 gene expression. Moreover, the gene expressions of Fas receptor and Fas ligand, but not p53, were also induced in HL-60 cells dose- and time dependently. It indicated that the activity of ceramide synthase is critical for the *P. urinaria*-induced apoptosis in HL-60 cells. The *P. urinaria*-induced apoptosis in HL-60 cells is mediated through a ceramide-related pathway [13].

The water extract of *P. urinaria* also significantly decreased the number of Lewis lung carcinoma cells in a dose-and time-dependent manner as determined by MTT assay. However, the water extract of *P. urinaria* did not exert any cytotoxic effect on normal cells such as endothelial cells and liver cells. Result from flow cytometry revealed a dose-dependent increase in dead cells 24 h after treating Lewis lung carcinoma cells with *P. urinaria* extract. The anticancer activity of *P. urinaria* extract was due to the apoptosis induced in Lewis lung carcinoma cells, which was demonstrated by DNA fragmentation analysis and increased caspase-3 activity. The apoptosis triggered by *P. urinaria* extract in Lewis lung carcinoma cells was associated with the down-regulation of Bcl-2 gene expression, but not with p53, p21 and Bax. *P. urinaria* extract induced the apoptosis of Lewis lung carcinoma cells, at least in part, through a mitochondria-associated intrinsic pathway [14].

IC_{50}

To study the potential anticancer effect of *P. urinaria* extract, the cell viability of LLC cells after P. urinaria treatment was analyzed by MTT assay. The number of LLC cells was reduced significantly by *P. urinaria* treatment dose- and time dependently. For 24-h treatment, IC_{50} value of *P. urinaria* extract on LLC cells was determined to be 2 mg/ml. Complete loss of cells could be observed with higher dose or longer exposure of *P. urinaria* extract. However, under same treatment, *P. urinaria* extract did not cause any cell loss in normal cells such as HUVECs and WRL 68 cells [14].

Side effect

Phyllanthus urinaria extract exhibited no cytotoxic effect on normal human cells, including vascular endothelial cells and liver cells. It implies that the aqueous extract of *P. urinaria* is substantially useful in treating various kinds of human cancer cells without toxic side effect on normal cells. It also implies that the pH or salt concentration of *P. urinaria* extract was physiologically tolerable by normal cells [13].

Panax ginseng

The herbal remedies referred to as "ginseng" are derived from the roots of several plants. One of the most commonly used and researched of the ginsengs is Panax ginseng, also called Asian/Korean ginseng. The main active components of Panax ginseng are ginsenosides, which have been shown to have a variety of beneficial effects, including anti-inflammatory, antioxidant, and anticancer effects. Results of clinical research studies demonstrate that Panax ginseng may improve psychologic function, immune function, and conditions associated with diabetes [15, 16].

Mechanism

It has been reported that Rh2 not only arrests the cell cycle of B16 melanoma cells at the G1/G0 phase, but also

stimulates melanogenesis in these cells. Previously, it was suggested that NK activity was modulated by Rh2. Although spleen cells from intact nude mice exhibited very weak NK activity, those from tumor-bearing nude mice at Days 21 and 28 showed a significant increase in the NK activity [17].

Angiogenesis is an important process in the promotion of cancer. Panax ginseng was found to have anti-angiogenic property [18].

IC_{50}

Ginsenoside Rh2 (Rh2), isolated from an ethanol extract of the processed root of Panax ginseng CA Meyer, inhibits the growth of B16 melanoma cells. Rh2 also inhibits proliferations of various established human ovarian cancer cell lines in a dose-dependent manner between 10 and 60 μM in vitro and induced apoptosis at around the IC_{50} dose (40 ± 5 μM). When mice were treated p.o. with Rh2 daily (but not weekly), the tumor growth was significantly inhibited, compared to cis-diamminedichloroplatinum(II) (CDDP) treatment alone. When Rh2 was combined with CDDP, the degree of tumor growth retardation was not potentiated. The survival time was significantly longer than that of medium alone-treated control. Then, whether p.o. administration of Rh2 has a dose-dependent inhibitory effect on the tumor growth was examined. I.p. and weekly administration of CDDP had more potent antitumor activity in the order of 1, 2, and 4 mg/kg, whereas p.o. and daily administration of Rh, (0.4–1.6 mg/kg) not only had antitumor activity comparable to that of 4 mg/kg CDDP, but also resulted in a significant increase in the survival. Doses of Rh2 used in this study did not result in any adverse side effects as confirmed by monitoring hematocrit values and body weight, unlike 4 mg/kg CDDP, which had severe side effects. It is noteworthy that p.o. but not i.p. treatment with Rh2 resulted in induction of apoptotic cells in the tumor in addition to augmentation of the natural killer activity in spleen cells from tumor-hearing nude mice. Thus, particularly in view of the toxicity of CDDP, Rh2 alone would seem to warrant further evaluation for treatment of recurrent or refractory ovarian tumor [17]. The absolute bioavailability of 20(S)-ginsenoside Rh1 in rats was only 1.01%.

Side effect

The toxicity of ginseng appears to be low: some of the reports of toxic episodes of ginseng may actually not pertain to ginsenosides, but to other components of multicomponent preparations. Very low incidence of toxicity has been observed in ginseng clinical trials using well-characterized preparations [16]. Overall, Panax ginseng appears to be well tolerated, although caution is advised about concomitant use with some pharmaceuticals, such as warfarin, oral hypoglycemic agents, insulin, and phenelzine [15]. Panax ginseng has the potential to significantly modulate the activity of drug-metabolizing enzymes (notably cytochrome P_{450} isozymes) and/or the drug transporter P-glycoprotein. It participates in potential pharmacokinetic interactions with anticancer drugs. It is advised that health care professionals and consumers should be aware of the potential for adverse interactions with Panax ginseng, question their patients on their use of them, especially among patients whose disease is not responding to treatments as expected, and urge patients to avoid herbs that could confound their cancer care [2]. Panax ginseng does not appear to enhance physical performance. Products with a standardized ginsenoside concentration are available [15].

Bupleurum scorzonerifolium

Plant Bupleuri Radix, a traditional Chinese medicine, has been used in various herbal mixtures such as Sho-Saiko-To and BZYQT. It has been shown to have a wide range of immunopharmacologic functions, such as anti-inflammatory, mitogenic, or antiviral activities. It was shown that the acetone extract of *B. scorzonerifolium* (AE-BS) can effectively inhibit the proliferation of lung cancer cells in vitro [19].

Mechanism

AE-BS can inhibit telomerase activity and induce apoptosis of human lung cancer cells. The induction of apoptosis may be via suppression of telomerase activity. The tumor cell growth was significantly inhibited by AE-BS (60 μg/ml) from the first day of culture, but normal lung fibroblasts were not significantly inhibited. In addition, numerous tumor giant cells are observed after treatment AE-BS, indicating that cell division was hindered. The results provide more evidence that telomerase activity has a role in chromosome separation during mitosis. This molecular mechanism may involve the potential role of telomerase inhibition in cancer treatment [19, 20].

IC_{50}

AE-BS showed a dose-dependent antiproliferative effect on the proliferation of A549 human lung cancer cells. The IC_{50} of AE-BS was 59 ± 4.5 μg/ml on day 1. The IC_{50} of AE-BS for WI38 human normal lung fibroblast cells, however, was significant higher than that for A549 cells (150 ± 16 μg/ml). After 72 h of exposure, AE-BS

(60 μg/ml) significantly reduced A549 cell proliferation to 33 ± 3.2% of control. A549 cells treated with AE-BS showed typical morphologic features of apoptosis, and the percentage of apoptotic cells was approximately 38% on day 1. AE-BS-treated cells demonstrated significantly lower telomerase activity on day 3. This result indicates that the AE-BS could suppress the proliferation of lung cancer cells via inhibition of telomerase activity and activation of apoptosis [19, 20].

Side effect

Bupleuri Radix is mildly toxic. Overdose can cause headaches, dizziness, vomiting, tremors, gastroenteritis, and pathogenic erections. There were reports of cases of mortality of broncho-interstitial pneumonia suspected were being caused by the combined use of *B. Radix* and interferon. Overdose can lead to kidney toxicity [7].

Adlay seed

Adlay seed is the seed of a plant that has been used as a traditional Chinese medicine [21]. The data showed that a methanolic extract, but not a water extract, of adlay seed exerted an antiproliferative effect on A549 lung cancer cells by inducing cell cycle arrest and apoptosis [22] and might prevent tobacco carcinogen-induced lung tumorigenesis [23].

Mechanism

The methanolic extract of adlay seed was tested for its regulation of COX-2 expression of human lung cancer cells. The methanolic extract of adlay seed inhibited basal and TPA-induced COX-2 expression in a dose-dependent fashion, whereas COX-1 expression was not affected. By using a promoter activity assay, it was found that the methanolic extract inhibited basal and TPA-stimulated COX-2 expression at the transcription level. The effect of the methanolic extract on COX-2 expression in vivo was then investigated. The data demonstrated that treatment of the methanolic extract reduced the PGE(2) level in serum and inhibited COX-2 expression of tumor tissues in nude mice. These results suggest that inhibition of COX-2 is one of the mechanisms by which the methanolic extract of adlay seed inhibits cancer growth and prevents lung tumorigenesis [23].

IC_{50}

It was also shown that tumor growth in vivo was inhibited by the methanolic extract in a dose-dependent manner. The chemopreventive effect of adlay seed on the tobacco-specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced lung tumorigenesis in A/J mice was also investigated. Diet containing 30% of powdered adlay seed reduced the number of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced surface lung tumors by approximately 50%. These results indicate that the components of adlay seed exert an anticancer effect in vitro and in vivo and may be useful for the prevention of lung tumorigenesis [22].

Side effect

There is no known side effect for adlay seed [22].

Hemsleya amabili

Hemsleya amabilis extract is a compound prepared from the plant named *Hemsleya amabilis*. *Hemsleya amabilis* has long been used in China to treat cancers as well as infectious diseases. However, the mechanisms of its anti-cancer abilities are barely understood. It was shown that *Hemsleya amabilis* extract significantly inhibited tumor cell growth, colony formation, and induced tumor cell apoptosis [24].

Mechanism

A reduction in cell growth and an induction in cell death are two major means to inhibit tumor growth. At low concentrations, *Hemsleya amabilis* extract caused significant inhibition of growth in U87 astrocytoma cell line, MDA-MB-231 breast cancer cell line, and Jurkat cells. These cells were derived from different tissue sources. The inhibitory effect of *Hemsleya amabilis* extract on cell growth implies that this compound may have a general function in anti-tumor cell growth. This is not unexpected, since cancer cells have developed the capacity of increased proliferation through a variety of growth signal pathways. This includes elevated external growth factors, increased intracellular matrix signal via integrin, and Ras protein mutation-derived constitutive mitogenic signals, resulting in growing neoplasm that causes destruction and atrophy of the surrounding tissue and adjacent organs. In a specific tumor, one pathway may play a more important role than the others. *Hemsleya amabilis* extract may act on more than one pathway. Nevertheless, different sensitivities of tumor cells to the growth-inhibitory effect of treatments of *Hemsleya amabilis* extract were noted. Jurkat cells, for example, which were poorly anchorage dependent in growth and survival, were less sensitive to the treatments when compared with U87 astracytoma cell line and

MDA-MB-231 breast cancer cells, which were anchorage dependent in growth. This is coincident with the findings that *Hemsleya amabilis* extract inhibited U87 cell spreading. These results suggest that *Hemsleya amabilis* extract may interfere with the interaction of tumor cells with extracellular matrix, or signals of the interaction [24].

IC_{50}

To investigate *Hemsleya amabili*'s anticancer activity, different types of cancer cells including human astrocytoma U87 cells, breast cancer cells MDA-MB-231, and Jurkat cells with *Hemsleya amabilis* extract were treated. This agent significantly inhibited tumor cell growth and colony formation at various concentrations. When astrocytoma cells were seeded in the presence of *Hemsleya amabilis* extract at very low concentrations, cell spreading was greatly inhibited. *Hemsleya amabilis* extract also promoted tumor cell death in all the tested cell lines, but with varied sensitivities. Apoptotic assays with Annexin V staining demonstrated that *Hemsleya amabilis* extract induced astrocytoma cell apoptosis at different concentrations [24].

The decrease in cell number treated with *Hemsleya amabilis* extract suggested cell death in the cell cultures. Cultures of the U87 astrocytoma cell line, MDA-MB-231 breast cancer cell line, and Jurkat cells were treated with *Hemsleya amabilis* extract at various concentrations for 24–72 h. The results indicated that *Hemsleya amabilis* extract had cytotoxicity on all the tumor cells tested. Twenty-four hours after the addition of *Hemsleya amabilis* extract, all tumor cells started dying. After 72-h incubation, cell death was obvious even at low concentration treatments. However, the sensitivities varied. U87 cells were the most sensitive to *Hemsleya amabilis* treatment: over 50% of cells died when treated with 25 μg/ml of *Hemsleya amabilis* extract. At this concentration, only 40% of MDA-MB-231 cells died, and a concentration of 50 μg/ml was required to obtain 50% cell death. Jurkat cells were the most insensitive group to *Hemsleya amabilis* treatment. To obtain 50% cell death, a concentration of 150 μg/ml *Hemsleya amabilis* extract was required [24].

Side effect

Among a variety of pro-apoptotic agents, plant-derived compounds such as *Hemsleya amabilis* are characterized by their multiple mechanisms and low side effects [24].

Ellipticine

The natural plant product ellipticine is an isolated compound. It was isolated in 1959 from the Australian evergreen tree of the Apocynaceae family. This compound was shown to be an extremely promising anticancer drug [25]. The planar polycyclic structure was shown to interact with DNA through intercalation, exhibiting a high DNA-binding affinity (10(6) M(-1)). The presence of protonatable ring nitrogens distinguished ellipticine from other simple intercalators. Both monocationic and uncharged species were found to be present under physiological conditions. The positive charge stabilized the binding of ellipticine to nucleic acids, while the more lipophilic uncharged compound was shown to readily penetrate membrane barriers. The structural nature of these compounds offers a plausible basis for the implication of multiple modes of action, including DNA binding, interactions with membrane barriers, oxidative bioactivation, and modification of enzyme function; most notably that of topoisomerase II and telomerase [25, 26].

Mechanism

Ellipticine is a potent antineoplastic agent whose mode of action is considered to be based mainly on DNA intercalation and/or inhibition of topoisomerase II. Ellipticine also forms covalent DNA adducts in vitro and that the formation of the major adduct is dependent on the activation of ellipticine by cytochrome P_{450} (CYP). The capacity of ellipticine to form DNA adducts in vivo was investigated. Male Wistar rats were treated with ellipticine, and DNA from various organs was analyzed by (32)P postlabeling. Ellipticine-specific DNA adduct patterns, similar to those found in vitro, were detected in most test organs. Only DNA of testes was free of the ellipticine-DNA adducts. The highest level of DNA adducts was found in liver (19.7 adducts per 10(7) nucleotides), followed by spleen, lung, kidney, heart, and brain. One major and one minor ellipticine-DNA adducts were found in DNA of all these organs of rats exposed to ellipticine. Besides these, 2 or 3 additional adducts were detected in DNA of liver, kidney, lung, and heart. The predominant adduct formed in rat tissues in vivo was identical to the deoxyguanosine adduct generated in DNA by ellipticine in vitro as shown by cochromatography in two independent systems. Correlation studies showed that the formation of this major DNA adduct in vivo is mediated by CYP3A1- and CYP1A-dependent reactions. The results show the formation of CYP-mediated covalent DNA adducts by ellipticine in vivo and confirm the formation of covalent DNA adducts as a new mode of ellipticine action [27].

Common molecular and cellular targets for ellipticine, isolated from well-known antitumor plants, have been studied and described. Other than DNA and other double helical polynucleotides, the followings are to be noted. 1. ATP synthesis in mitochondria. Most of DNA intercalators,

including sanguinarine and ellipticine, belong to a group of penetrating (hydrophobic) cations, which are accumulated near the external side of inner mitochondrial membranes during the membrane energization. They neutralize negative charges, arising just as the inner mitochondrial membranes become energized. By this neutralization of membrane charges, the ATP synthesis is inhibited and the oxidative phosphorylation renders to be uncoupled. All studied DNA intercalators under certain conditions uncouple the mitochondrial oxidative phosphorylation. Apparent correlation between the agents' ability for DNA intercalation and for mitochondrial ATP synthesis inhibition seems to be determined by the importance for both types of reactions of molecule hydrophobicity and positive charges. 2. Cholinesterase systems. Ellipticine and some of their derivatives, like other DNA intercalators studied, inhibit also the enzymatic activities of cholinesterase systems due to hydrophobicity and positive charges of their molecules [28].

IC_{50}

A panel of genetically engineered V79 cell lines including the parental line V79MZ and recombinant cells expressing the human CYP enzymes CYP1A1, CYP1A2, or CYP3A4 were evaluated for their ability to activate ellipticine. The extent of activation was determined by analyzing DNA adducts by 32P-postlabeling. Ellipticine was found to be toxic to all V79 cell lines with IC_{50} values ranging from 0.25 to 0.40 μM. The nuclease P1 version of the 32P-postlabeling assay yielded a similar pattern of ellipticine–DNA adducts with two major adducts in all cells, the formation of only one of which was dependent on CYP activity. This pattern is identical to that detected in DNA reacted with ellipticine and the reconstituted CYP enzyme system in vitro as confirmed by HPLC of the isolated adducts. Total adduct levels ranged from 2 to 337 adducts per 10(8) nucleotides, in the parental line and in V79 expressing CYP3A4, respectively. As in vitro, human CYP1A2 and CYP1A1 were less active. The results presented here show the formation of CYP-mediated covalent DNA adducts by ellipticine in cells in culture and confirm the formation of covalent DNA adducts as a new mechanism of ellipticine action [29].

Side effect

Pharmacologically, a number of toxic side effects occur, but the amenability of ellipticine toward systematic structural modification has permitted the extensive application of rational drug design. A number of successful ellipticine analogs have been designed and synthesized with improved toxicities and anticancer activities. More recently, the synthetic focus has broadened to include the design of hybrid compounds, as well as drug delivery conjugates. Considerable research efforts have been directed toward gaining a greater understanding of the mode of action of these drugs that will help further in the optimization of drug design [25].

The antitumor drug celiptium (N2-methyl-9-hydroxyellipticinium) is an ellipticine derivative effective in experimental tumors and in man. The major side effect is nephrotoxicity. The impairment of renal function is studied in rats following a single i.v. dose of 20 mg/kg celiptium and a long-term study (day 2–day 60). A loss of body weight is noted in celiptium-treated animals between day 4 and day 15, and recovery occurs between day 15 and day 60. Histologic study shows cortical lesions characterized by focal necrosis of proximal tubules without any glomerular, interstitial, and vascular alterations on day 8. It is to be noted that any medullary lesions were not shown. A polyuria and a decreased creatinine clearance are reported on day 8. Rats were water deprived between day 6 and day 8 following celiptium administration. The decrease in urinary osmolality is not recovered after dehydration, and exogenous vasopressin derivative (dD AVP) does not correct the renal concentration defect. AVP plasma levels increase after dehydration. These results imply a pitressino-resistant urinary concentrating inability in celiptium-treated rats [29]. The main reason for the interest in ellipticine and its derivatives for clinical purposes is their high efficiencies against several types of cancer, their rather limited toxic side effects, and their complete lack of hematologic toxicity. Nevertheless, ellipticine is a potent mutagen. Most ellipticines are mutagenic to *Salmonella typhimurium* Ames tester strains, bacteriophage T4, *Neurospora crassa*, and mammalian cells and induce prophage lamda in *Escherichia coli* [27].

Embelin

Embelin, an isolated plant-based benzoquinone derivative from the Japanese Ardisia herb, has been shown to exhibit significant antitumor activity in methylcholanthrene-induced fibrosarcoma in albino rats besides enhancing their survival time [30].

Mechanism

The X-linked inhibitor of apoptosis (XIAP) is a promising new molecular target for the design of novel anticancer drugs aiming at overcoming apoptosis resistance of cancer cells to chemotherapeutic agents and radiation therapy. Recent studies showed that the BIR3 domain of XIAP where caspase-9 and Smac proteins bind is an attractive

site for designing small-molecule inhibitors of XIAP. It was discovered embelin as a small-molecular weight inhibitor that binds to the XIAP BIR3 domain. Embelin binds to the XIAP BIR3 protein with an affinity similar to that of the natural Smac peptide using a fluorescence polarization-based binding assay. NMR analysis further conclusively confirmed that embelin interacts with several crucial residues in the XIAP BIR3 domain with which Smac and caspase-9 bind. Embelin inhibits cell growth, induces apoptosis, and activates caspase-9 in prostate cancer cells with high levels of the XIAP but has a minimal effect on normal prostate epithelial and fibroblast cells with low levels of XIAP. In stably XIAP-transfected Jurkat cells, embelin effectively overcomes the protective effect of XIAP to apoptosis and enhances the etoposide-induced apoptosis and has a minimal effect in Jurkat cells transfected with vector control. Taken together, embelin is a fairly potent, non-peptidic, cell-permeable, small-molecule inhibitor of XIAP and represents a promising lead compound for designing an entirely new class of anticancer agents that target the BIR3 domain of XIAP [31, 32].

IC_{50}

The effect of embelin on cell growth in prostate cancer cells (PC-3 and LNCaP) versus normal cells was evaluated. Embelin inhibited cell growth of both PC-3 and LNCap cells in a dose-dependent manner, with IC_{50} values of 3.7 and 5.7 μM, respectively. To evaluate its selectivity, its activity in normal PrEC and in WI-38 cells was also tested. The IC_{50} values were found to be 20.1 μM and 19.3 μM in normal PrEC and in WI-38 cells, respectively. Thus, embelin appears to display certain selectivity for cancer cells with high levels of XIAP versus normal cells with low levels of XIAP [31].

Jurkat cells stably transfected with XIAP (Jurkat-XIAP cells) become resistant to apoptosis induced by etoposide when compared to Jurkat cells transfected with vector control (Jurkat-Vec cells), indicating that XIAP overexpression protects Jurkat cells from etoposide-induced apoptosis. Consistent with the apoptosis assay, Jurkat-XIAP cells also become less sensitive to etoposide in cell growth assay than Jurkat-Vec cells. While 94.3 ± 0.6% of Jurkat-Vec cells were killed with 2.5 μM of etoposide for 72 h, only 59 ± 2% Jurkat-XIAP cells were killed under the same conditions. Increasing the concentration of etoposide to 10 μM only killed 85 ± 0.1% Jurkat-XIAP cells. These results demonstrated that XIAP overexpression protects the transfected Jurkat cells from etoposide-induced apoptosis and cytotoxicity. The response of Jurkat-Vec and Jurkat-XIAP cells to embelin in cell growth assays was evaluated. As expected, embelin only has a weak activity in Jurkat-Vec cells (IC_{50} = 20 μM). Intriguingly, embelin also has a weak activity in Jurkat-XIAP cells, essentially identical to that in Jurkat-Vec cells. Of note, both Jurkat-Vec and Jurkat-XIAP cells unlikely depend on the protective effect of XIAP for survival since the parental Jurkat cells have a very low level of XIAP protein. Thus, treatment of Jurkat-Vec and Jurkat-XIAP cells which do not rely on XIAP protein for survival with a small-molecule inhibitor of XIAP such as embelin is not expected to effectively achieve cell growth inhibition or induce apoptosis [31].

Side effect

Overdose can lead to kidney toxicity [7].

Curcumin

Ingestion of plant products containing the phenolic phytochemical, curcumin, has been linked to lower incidences of colon cancer, suggesting that curcumin has cancer chemopreventive effects [33]. Curcumin, a naturally occurring pigment, isolated from the rhizome of the plant *Curcuma longa* has been shown to have anti-inflammatory, antioxidant, and anti-cancer activities [34]. Curcumin is a major component of the spice turmeric. Due to its presence in the diet, one of its primary targets is the human gastric mucosa cells [35].

Mechanism

Curcumin inhibits lipooxygenase activity and is a specific inhibitor of cyclooxygenase-2 expression. Curcumin inhibits the initiation of carcinogenesis by inhibiting the cytochrome P_{450} enzyme activity and increasing the levels of glutathione-S-transferase. Curcumin inhibits the promotion/progression stages of carcinogenesis. The anti-tumor effect of curcumin has been due in part to the arrest of cancer cells in S-phase, G2/M cell cycle phase, and induction of apoptosis. Curcumin inhibits the growth of DNA mismatch repair defective colon cancer cells. Therefore, curcumin may have value as a safe chemotherapeutic agent for the treatment of tumors exhibiting DNA mismatch repair deficient and microsatellite instable phenotype [36].

Mitogen-activated protein kinase (MAPK) and nuclear factor kappa B (NF-kappaB) signaling cascades are thought to regulate apoptosis and cell survival. While curcumin inhibits NF-kappaB, its effects upon MAPK pathways are unclear. Curcumin effects upon MAPK signaling and apoptosis in HCT116 cells were investigated. Curcumin time- and dose-dependent induction of apoptosis was accompanied by sustained phosphorylation and activation of c-jun N-terminal kinase and p38 MAPK as well as inhibition of constitutive NF-kappaB transcriptional

activity. Curcumin treatment also induced c-jun N-terminal kinase dependent sustained phosphorylation of c-jun and stimulation of AP-1 transcriptional activity. It was shown that c-jun N-terminal kinase, but not p38 or ERK signaling, plays an important role in curcumin-mediated apoptosis in human colon cancer cells that may underlie its chemopreventive effects [37, 38].

12-O-Tetradecanoyl phorbol-13-acetate (TPA) is a strong promoter of chemically induced skin cancer. The exact mechanism by which TPA promotes skin cancer is not clear. However, it is known that TPA elevates the expression of oncogenes involved in cell proliferation. Recently, it has been shown that curcumin significantly inhibits TPA-induced tumor promotion on mouse skin. However, the mechanism by which curcumin inhibits TPA-induced tumor promotion is not known. The effect of curcumin on the expression of c-fos, c-jun, and c-myc oncogenes in TPA-treated mouse skin in CD-1 mice was investigated. A 30-nmol dose of TPA increased the levels of mRNAs for c-fos, c-jun, and c-myc oncogenes by two to threefold compared with control. Topical application on the dorsal side of the skin with 1, 10, 20, or 30 mumol of curcumin 30 min before TPA treatment inhibited the TPA-induced expression of these proto-oncogenes. Inhibition of expression of c-fos and c-jun was more pronounced than that of c-myc. A dose of 10 mumol of curcumin was shown to inhibit 90% TPA-induced expression of c-fos and c-jun, and 60% of c-myc. These data strongly suggest that curcumin may inhibit skin cancer through the modulation of expression of these proto-oncogenes [39].

To identify a potential pro-apoptotic gene that could be responsive to the DNA damage in curcumin-treated cells, growth arrest and DNA damage-inducible gene 153 (GADD153) was considered. Curcumin increased GADD153 mRNA (and also protein) expression. These findings suggest that curcumin-induced upregulation of GADD153 mRNA expression was at the level of transcription, but apparently without depending on upstream MAPK. In determining the involvement of reactive oxygen species in mediating the effect of curcumin on GADD153, the antioxidants pyrrolidine dithiocarbamate and *N*-acetylcysteine, but neither alpha-tocopherol nor catalase, also blunted or prevented upregulation of GADD153 mRNA expression caused by curcumin. Because expression of GADD153 protein was detected before the appearance of apoptotic features, this observation raises the possibility that GADD153 protein might be important for curcumin-induced apoptosis [40].

IC_{50}

Curcumin at of 15, 25, and 50 μM caused DNA damage in GM cells and human peripheral blood lymphocytes. There was no difference between the extent of the damage in both types of cells. Damaged cells were able to recover within a period of 120 min. Curcumin may play a dual role in carcinogenesis [35]. The cellular and molecular changes induced by curcumin leading to the induction of apoptosis in human lung cancer cell lines-A549 and H1299 were investigated. The IC_{50}s at 24-h exposure of curcumin were 50 and 40 μM for A549 and H1299 cells, respectively. A549 is p53 proficient and H1299 is p53 null mutant. The lung cancer cells were treated with curcumin (0–160 μM) for 12–72 h. Curcumin inhibited the growth of both the cell lines in a concentration-dependent manner. Growth inhibition of H1299 cell lines was both time and concentration dependent. Curcumin induced the apoptosis in both lung cancer cell lines. A decrease in expression of p53, bcl-2, and bcl-X(L) was observed after 12-h exposure of 40 μM curcumin. Bak and caspase genes remained unchanged up to 60 μM curcumin but showed decrease in expression levels at 80–160 μM. The data also suggest a p53-independent induction of apoptosis in lung cancer cells [34].

Curcumin significantly inhibited the growth of AGS human gastric carcinoma cells in a dose- and time-dependent manner. Curcumin caused a 34% decrease in AGS proliferation at 5 μmol/l, 51% at 10 μmol/l, and 92% at 25 μmol/l after 4 days of treatment. When curcumin (10 μmol/l) was removed after a 24-h exposure, the growth pattern of curcumin-treated AGS cells was similar to that of control cells, suggesting reversibility of curcumin on the growth of AGS cells. After 4 days of treatment with 10 μmol/l of curcumin, the G2/M phase fraction of cells was 60.5% compared with 22.0% of the control group, suggesting a G2/M block by curcumin treatment. Because the curcumin concentrations (5 μmol/l) used were similar to steady-state concentrations (1.77 ± 1.87 μmol/l) in human serum of subjects receiving chronic administration of a commonly recommended dose (8 g/day), curcumin may be useful for the treatment of gastric carcinoma [40]. In healthy subjects, the mean peak concentration of curcumin achieved from dosing 650 mg of curcumin was 22.43 ng/ml.

Side effect

Curcumin has been widely used for centuries in the Asian countries without any toxic effects [40]. Reported side effects are uncommon and are generally limited to mild stomach distress. There is some evidence that turmeric extracts can be toxic to the liver when taken in high doses or for a prolonged period of time. There is a possibility of allergic contact dermatitis from turmeric. It should be avoided during pregnancy [7]. A dose-limiting side effect of anticancer therapy in the gastrointestinal tract is mucosal barrier injury. It is hypothesized that mucosal barrier injury is initiated and amplified by proinflammatory-and

NF-kappaB-regulated mediators. Therefore, the effect of NF-kappaB inhibition was studied in the onset of mucosal barrier injury. In response to cytostatic drug treatment (arabinoside cytosine and methotrexate), NF-kappaB was activated in intestinal epithelial cells resulting in an NF-kappaB-related induction of tumor necrosis factor alpha and monocyte chemoattractant protein-1. NF-kappaB inhibition increased the susceptibility of intestinal epithelial cells to arabinoside cytosine as well as methotrexate-induced cell death when obtained by the addition of caffeic acid phenethyl ester, but not using curcumin. In an animal model for methotrexate -induced mucosal barrier injury, the induction of NF-kappaB-related cytokines and chemokines was detected upon treatment with methotrexate. Despite increased susceptibility shown in vitro, the inhibition of NF-kappaB resulted in a partial amelioration of villous atrophy normally seen in the small intestine upon methotrexate treatment. These results show that the inhibition of NF-kappaB does not increase intestinal side effects of the anticancer treatment, suggesting a safe use of curcumin and caffeic acid phenethyl ester (another NF-kappaB inhibitor) is in combination with anticancer treatment [41].

Conclusion

These natural plants and isolated compounds are useful in treating cancer. It is important to appreciate the importance of these agents in treating cancer. Each agent has its own pros and cons. Please consult your physician first before deciding the suitability to use any of these materials.

Acknowledgments I sincerely wrote this article in memory of Dr. Neil Towers, who passed away in the morning of November 15, 2004. This is to hope that Dr. Neil Towers's work ethics, goals, and dreams live on by me. Dr. Neil Towers was a Pergamon Phytochemistry Prize recipient.

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