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Herbal Medicine in the Treatment of Cancer

John W. Ho*, Yuet Kin Leung and Chun Pong Chan

Department of Biochemistry and Environmental Science Programme, The Chinese University of Hong Kong, Shatin, Hong Kong

Abstract: Many of the classes of phytochemicals in herbal medicine are finding therapeutic use. In particular, cancer patients are reported to benefit from treatment with herbal medicine and survivability in many cases is significantly enhanced. Recent studies showed the anti-oxidative and superoxide scavenging activities of individual active components of herbal medicine for their inhibitory activities on lipid peroxidation and anti-cancer properties. Individual herbal medicines show antipyretic, analgesic and anti-inflammatory and anti-cancer effects. In addition to sharing many therapeutic activities, herbal medicine is also used in nutrient supplement for anti-cancer and anti-inflammatory activity. Numerous *in vitro* studies of herbal medicine on different cell lines and *in vivo* study of herbal medicine have been reported. However, the mechanisms of actions remain unclear. This review aims to give an overview on the recent development of herbal medicine in the prevention and treatment of cancer. The report covers the possible mechanism of action of some of the herbal medicine. In addition, the common properties of herbal medicine are described. Finally, the study sheds lights on the pharmacological applications of herbal medicine in the treatment of cancer and its potential use as anti-cancer agents.

INTRODUCTION

Herbal medicine has been widely used for treatment of different diseases in China for hundreds of years. Herbal medicines usually are prepared in a traditional formulation that contains a variety of constituents such as triterpenoids, flavonoids, a saponin-like glycoside, flavonoid glycosides such as liquiritin and rhamnoliquirtin, coumarin derivatives including herniarin. Different formulations have spasmolytic properties and beneficial influences on the healing process of ulcers. Other therapeutic properties of herbal medicines include anti-inflammatory, antiallergic, antiarthritic, antiestrogenic, antihepatoxitic, antiviral and anticholinergic actions. However, herbal medicine is hampered by its quality and often its authenticity. In addition, our limited understanding of their biological activities and the slow action in the healing process has slowed down the development of herbal medicine for pharmacological applications. Nevertheless, recent development of herbal medicine for prevention or treatment of cancer has aroused a lot of interest and research in this area. This review describes some biological therapies with herbal medicines used primarily or exclusively against cancer and its treatment and represents reports on herbal medicine available to prevent or to treat cancer. They are selected because they are among those of most recent and popular interest in the treatment of cancer today.

Herbal medicines have been used increasingly in Western countries. The design of formulation is an iterative process of activity-directed composition and isolation of natural principal constituents, and to develop an efficacious composition of lead compounds of herbs. New drugs can be developed from herbal medicine. A recent study showed that herbal preparation consisted of extracts from eight herbs was used with increasing frequency by prostate cancer patients worldwide [1]. Evidence has revealed that this formulation is an effective modality that could alleviate some symptoms even in majority of advanced prostate cancer patients. Some of these cases failed conventional therapy. The effectiveness of this herbal formulation in prostate cancer is believed to be due to its complex composition which can target many signal transduction and metabolic pathways and, consequently, reduce cancer cell growth. The *in vitro* studies reveal its effect, on the cell cycle specificity, induction of apoptosis and androgen receptor as well as molecular and metabolic changes induced by this herbal medicine. Individual chemical components present in the herbal formulation are known to have antiproliferative, anti-cancer and differential in induction activity [1]. Alkaloids isolated from herbal medicinal plants generally have therapeutic applications. Camptothecin (CPT) is isolated from the stem wood of the Chinese tree, Camptotheca acuminata. It is an alkaloid exhibiting, antileukemic and antitumor activities [2]. Camptothecin and two of its analogs Fig. (**1**) inhibited topoisomerase I with an IC_{50} value 2-fold higher than CPT. These two analogs had similar cytotoxicity against the KB cell line, although the two analogs showed significant difference in the protein-linked DNA breaks in KB cells. Cross-resistance with the two analogs was seen in a VP-16-resistant KB subline, which showed down-regulation of topoisomerase II and over expression of the multiple drug resistance-associated protein [2]. Cell cycle analysis demonstrated that these analogs had similar effects on cell cycle of KB. These results suggested that they exerted their cytotoxicity through topoisomerase I. However, *in vivo* study showed that the analog of camptothecin-amino-O-demethylepipodophyllotoxin was more effective against the growth of human prostate cancer cells in nude mice than

*Address corresponding to this author at the Department of Biochemistry and Environmental Science Programme, The Chinese University of Hong Kong, Shatin, Hong Kong; Fax: 852-2603-7732; E-mail: b678738@mailserv.cuhk.edu.hk

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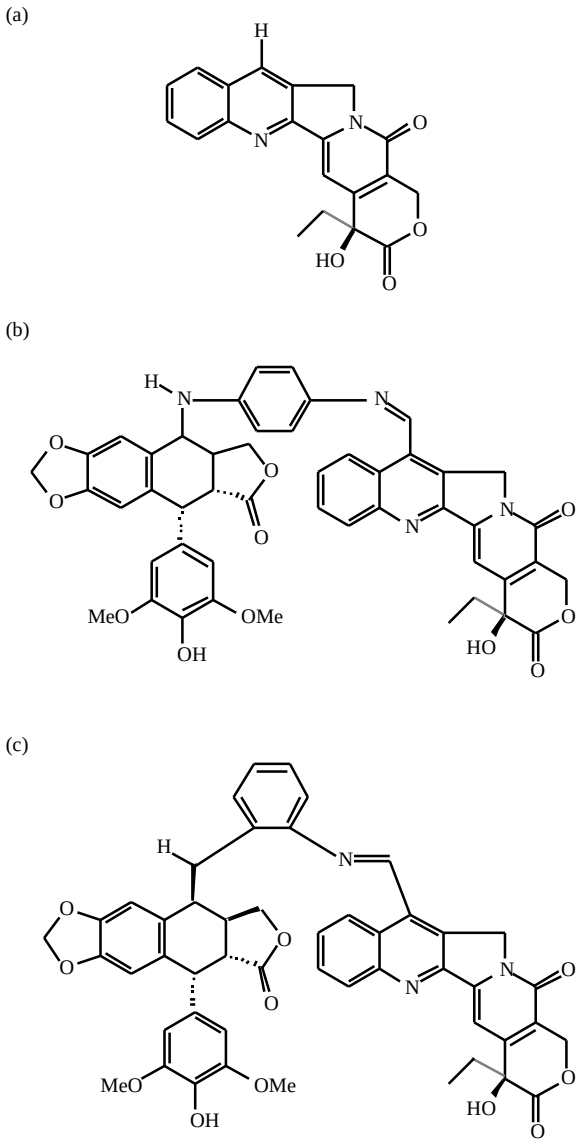

Fig. (1). Chemical structures of (a) Camptothecin, (b) Camptothecin-(para)-4β-amino-4'-O-demethylepipodophyllotoxin, (c) Camptothecin-(ortho)-4β-amino-4'-O-demethylepipodophyllotoxin

CPT. Inhibition of cancer cell growth is a common approach to treat cancer. Recently, it was reported that the aqueous extract of Coptidis rhizoma had potent inhibitory effect on the proliferation of esophageal cancer cells (ECCs) lines after treatment for 72 hr [3]. The extract and berberine Fig. (**2**), one of the major principles of Coptidis rhizoma showed potent antitumor effects on ECC lines [3]. Cell cycle analysis of Coptidis rhizoma-treated cancer cells showed the accumulation of cells in the G_0/G_1 phase. The results indicate Coptidis rhizoma was an effective inhibitor on proliteration of esophageal cancer cell lines. More recently, Coptidis rhizoma was reported to demonstrate induction of *rcl*, a novel growth-related gene in rat H4IIE cell line [4]. Rat hepatoma cell viability after treatment with an aqueous extract of Coptidis rhizoma was reduced. However, the treatment with Coptidis rhizoma extract increased the

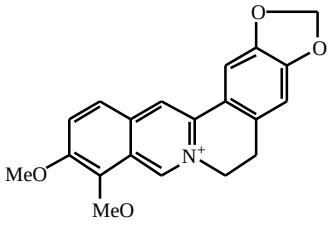

Fig. (2). Chemical structure of berberine

expression of a putative c-myc-responsive gene *rcl*. The results suggested that the extract could increase the activity of some transcription factor in inhibiting the growth of cancer cells. The increase was accompanied by an increment in the expression of mRNA for c-Myc-responsive gene. Deregulation of the c-Myc oncogene is prevalent in various human cancers [5-6]. The c-Myc protein participates in the regulation of cell proliferation, differentiation, and apoptosis [7]. The mechanism by which c-Myc induces neoplastic transformation and apoptosis is only beginning to emerge from studies of c-Myc target genes and signal transduction pathways [8]. Similarly, effects of berberine from Coptidis rhizoma on the viability of H4IIE cell lines and the induction of *rcl* mRNA in H4IIE cells were observed. However, the effects of berberine alone were about 15% lower than that of the aqueous extract of Coptidis rhizoma but the cytotoxicity of berberine was different against normal cells and cancer cells (Fig. (**3**)). Although the mechanism of its action is lacking, it is believed that Coptidis rhizoma induces a transient suppression of c-Myc mRNA, which correlates with growth inhibition of cancer cells. Although apoptosis was evident 48 hr after initiating Coptidis rhizoma exposure, the primary phase of cell death, which occurred during the first 24 hr was believed to be non-apoptotic. These studies indicate that non-apoptotic pathways can also regulate cell death in the cancer cells and support the role of c-Myc expression and c-Myc protein. Another study showed that Coptidis rhizoma and Ogon (Scutellariae radix) inhibited azoxymethane (AOM)-induced aberrant crypt foci (ACF) formation [9]. The mechanism of its biological activity is believed to affect cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) activities [9]. Both herbal medicine inhibited COX-2 but not COX-1 which subsequently exerted suppressive effects on ACF development. The results suggested that Coptidis rhizoma in the herbal formulation showed chemopreventive properties for colon cancer. In addition, crude extracts from nine plants commonly used in Mexican traditional medicine for the treatment of cancer have been reported to exhibit cytotoxic activity against human tumor cells [10]. The extracts of Colubrina acrocarpa (Rhamnaceae), Acacia pennatula (Leguminosae) and Hemiangium excelsum (Hippocrateaceae) exhibited significant cytotoxic activity. The study suggested different degree of drug selectivity on cell types. Like any other drugs, treatment with herbal medicine will be made more effective if an appropriate formulation can be developed.

Among different herbal medicines used in traditional formulations, licorice is a highly valued herb in Chinese medicine and has gained popularity in the West during the last decade. There is a voluminous literature on the

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beneficial effects of licorice and its constituents which demonstrate its ability to target a myriad of tissues, producing an array of pharmacological responses. Licorice root extract has been used in folkloric medicine for treatment of cancer. The variety of phytochemicals from licorice possess anti-inflammatory and immune modulating activity. The major classes of phytochemicals found in licorice root extract include triterpenoids, chalcones, isoflavones, coumarins, acetophenones, flavonoids and phenolic acids (Fig. (**4**)). Despite the biological activities reported for licorice root extract and constituents such as glycyrrhizin, the major use of licorice extract entails palatability enhancement of bitterness in herbal formulation and immune responses. Previous work showed that glycyrrhizin displayed a number of pharmacological effects including anti-tumor promotion [11] and immunoregulatory activities [12-13]. However, the mechanism of its action remains sketchy. Earlier work showed that the induction with licorice extract enhanced NO being released from macrophases [14-15]. The NO released from macrophages is a mediator of microbicidal [15] and tumoricidal activity [16]. It was reported that nitric oxide from macrophages [16] and Kupffer cells [17] kills tumor cells. The ability to stimulate macrophages to produce nitric oxide resided on the membraneous fragment of the tumor cells. Glycyrhizin did not induce NO from unstimulated macrophages. However, glycyrrhzin increased the production of nitric oxide by IFN-γ-stimulated macrophages. The NOS mRNA was increased by the addition of glycyrrhizin to the cell culture stimulated with a lower amount of IFN-γ [18]. It is believed that glycyrrhizin worked synergistically with IFN-γ to induce NO production of macrophages. However, many mechanisms of licorice activity are still unknown. Since the major constituents of licorice produce effects that are different from one another, and a single principle could initiate multiple actions in the same tissue, the overall pharmacology of licorice is complex. The ability of licorice to target multireceptor systems at the membrane, and to activate intracellular steroid receptors, may explain the complex pharmacological effects of licorice [18]. On the other hand, its effects on cellular immunocompetence of gamma ray-irradiated mice have been reported [19]. It was showed that glycyrrhizae (GL) and glycyrrhizic acid (GA) of the licorice extract exhibited cellular immunocompetence in irradiated mice. The blastogenic responses of splenocytes to mitogens including PHA and Con A were detected [19]. However, the blastogenic responses of splenocytes to mitogens were inhibited by gamma-ray irradiation. GL and GA were effective in enhancing the recovery of leukocyte count and the blastogenic responses due to gamma-ray irradiation. The study showed that GL and GA can help the recovery of the cellular immunocompetence in mice after gamma-irradiation. Licorice has undoubtedly effects on the immune responses in cells in the treatment of cancer. Recent study also showed that licorice had effects on the expression of UDP-glucuronosyltransferases (UGTs) in rat hepatoma cells [20]. UGTs are important in elimination of endo- and xenobiotics via glucuronidation reaction. The mRNA of UGTs showed noticeable increase after treatment with licorice extract or glycyrrihizin, the active principle of licorice to a lower extent. The results suggested that licorice exhibited differential induction of UGTs through transcriptional regulation of the genes associated with UGTs. However, the detail mechanism of its action is lacking. Another antitumor agents, Kansuiphorins A and B (Fig. (**5**)), were isolated from Euphorbia kansui [21]. The extract of the roots has been widely used in herbal medicine for the treatment of cancer. The extract exhibited antileukemic activity

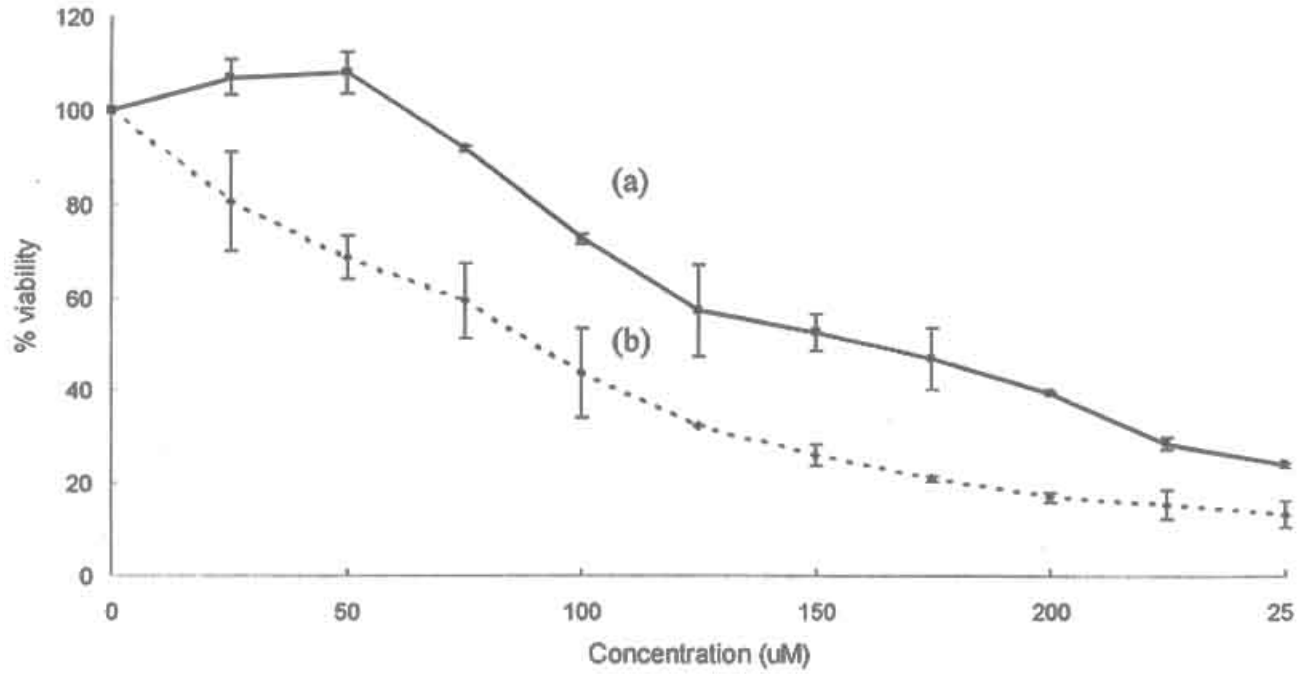

Fig. (3). Cytotoxicity of berberine towards (a) Clone 9, (b) H4IIE cells.

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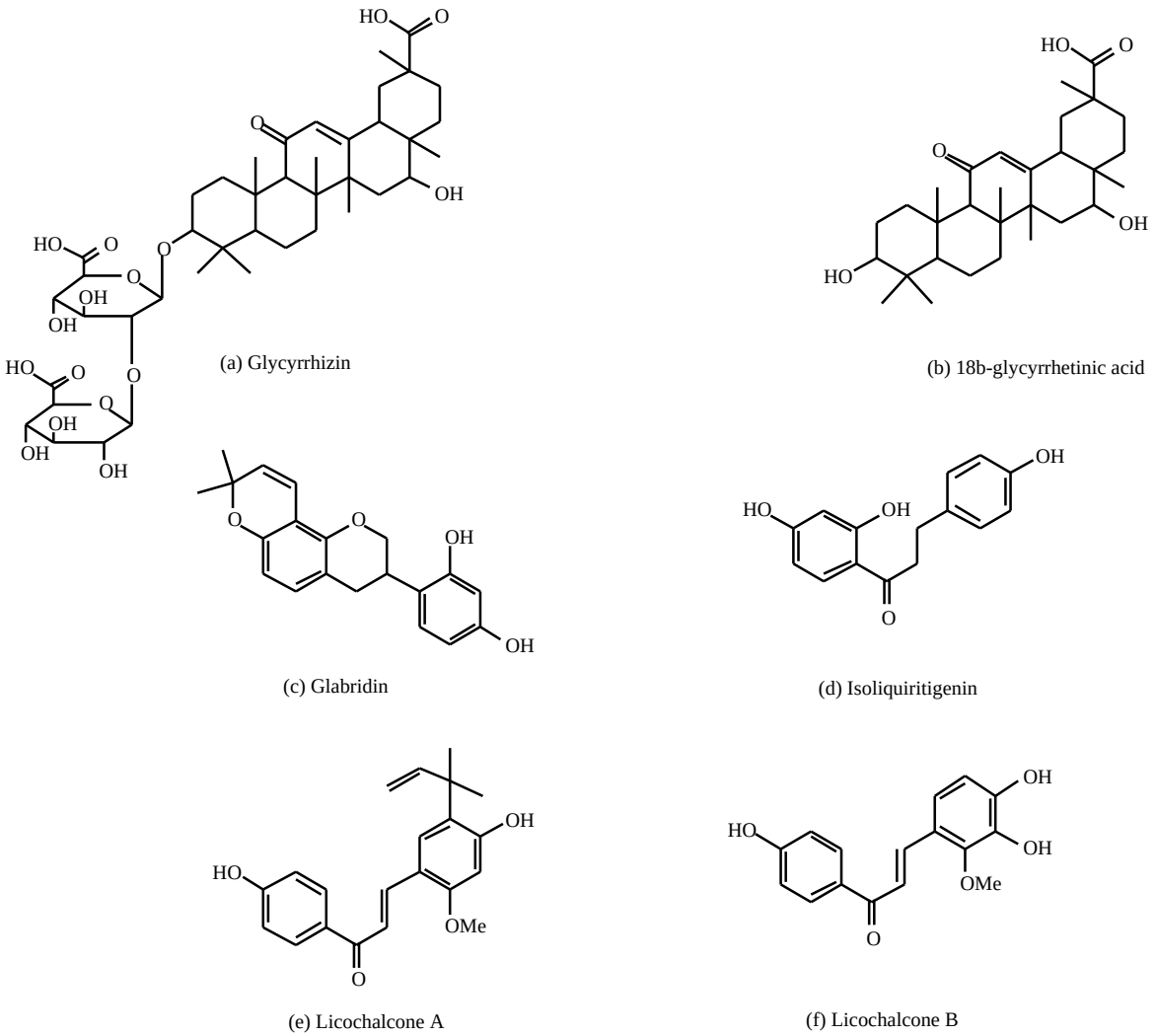

Fig. (4). Chemical structures of principles of licorice

against lymphocytic leukemia in mice. Kansuiphorin A (13-hydroxy-ingenol-3-(2, 3-dimethylbutanonate)-13-dodecano-ate-20-hexadecanoate) and kansuiphorin B (6,7-epoxy-13-hydroxyingenol)-3 (2,3-dimethylbutanoate)-13-dodecanoate-20-hexadecanoate), the two major active components of Euphorbia kansui were chemically characterized [21]. Both compounds demonstrate potent antileukemic activity. However, kansuiphorin A inhibited the growth of a particular disease-oriented human cancer cell lines. Nevertheless, the mechanism of its action is not known.

Among herbal medicines used for treatment of cancer, agricultural fruits especially the dried products such as grapes are commonly used in herbal formulation. A recent study showed that trans-resveratrol as shown in Fig. (**6**), a natural stibene present in wine and grapes exhibited antiinflammatory and anticancer activities [22]. The surge of interest in using nonsteroidal anti-inflammatory drugs (NSAIDs) to protect against colon and other cancer is the outgrowth of important findings that the body has two forms of cyclooxygenase which can be inhibited by NSAIDs [23]. However, it soon became clear that only COX-2 is important for inflammation. The function of COX-2 is to convert arachidonic acid, a long-chained fatty acid to prostaglandins, which subsequently trigger inflammatory reactions in the body. COX-1, the other cyclooxygenase also makes prostaglandins, but they are needed to maintain the stomach lining and kidney function. The study led to a new generation of drugs that inhibit only COX-2 which are the focus of cancer trials. Previous study reported that a phenolic antioxidant found in grapes and wine, inhibited phorbol ester (PMA)-mediated induction of COX-2 in human mammary and oral epithelial cells [24]. However, these effects were inhibited by resveratrol. Resveratrol inhibited protein kinase (PKC) and the induction of COX-2 promoter activity by c-June as well as AP-1 activity. Resveratrol-induced apoptosis following 4 hr treatment was confirmed by flow cytometry at concentrations as low as 1 μM and 100 nM in the assay for detection of membrane phosphatidylserine. Resveratrol – treated cells did not produce tumor necrosis factor alpha protein. This observation suggested that resveratrol is an important cofactor in nonspecific immune reactions in anticancer activity. The results suggested resveratrol played an important role in anti-cancer activity.

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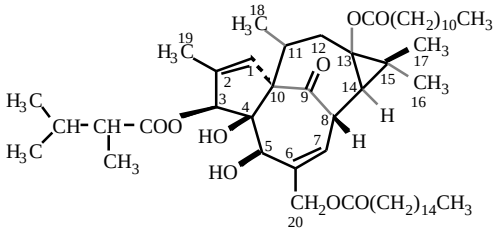
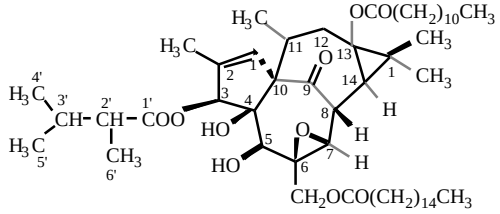
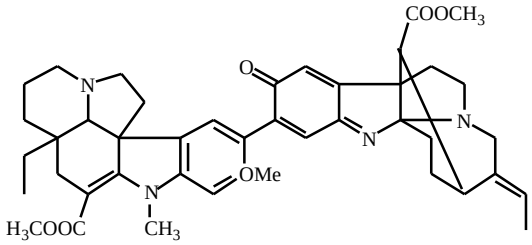


(a) Kansuiphorin A

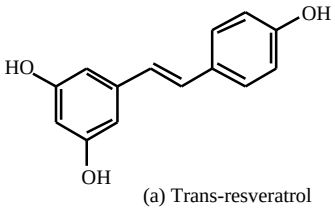


(b) Kansuiphorin B

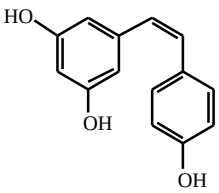


(c) Vincarubine

Fig. (5). Chemical structures of kansuiphorin A and B, and vincarubine



(a) Trans-resveratrol



(b) Cis-resveratrol

Fig. (6). Chemical structure of resveratrol

In search for antitumor substances from herbal medicine, sinococuline (Fig. (**7**)), an morphinane alkaloid from Cocculus trilobus (Menispermaceae) was isolated in

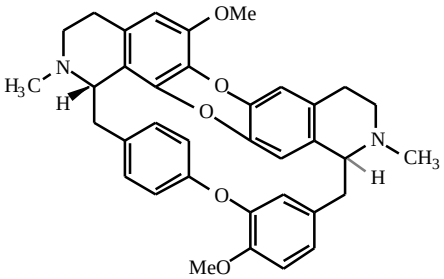


Fig. (7). Chemical structure of sinococuline

methanol [25]. It showed a remarkable inhibition on sarcoma 180 ascites in mice. Sinococuline, the active principle of the methanol extract belongs to the group of morphinane alkaloids. Sinococuline had antitumor effect on P388 Leukemia [25]. However, the detail mechanism of its action is lacking.

Vinca minor L. is a medicinal plant used as an ingredient of a formulation in preparation of folk medicine for treatment of cancer. Its biological activity on cancer cell and its functions remain unclear. However, it is believed that Vina minor L. could stimulate the blood flow in the brain [26]. To maintain a good blood circulation is an important approach in the treatment of cancer with herbal medicine. Among monomeric indole alkaloids isolated from the leaves of Vina minor L. (little periwinkle), the gross structure of vincarubine (Fig. (**5**)), the first bisindole base of this plant species was described [27]. Vincarubine can form a dimer consisting of a vincorane moiety represented by an oxygenated form of 10-O-demethyl-1-norvincorine, and 11-methoxy-1-methylvincadifformine. These moieties can be considered as the building block for vincarubine [28]. Some monomeric indole alkaloids isolated from the leaves of little periwinkle showed cytotoxic activity on P388 leukemic cells [29]. Vincarubine was reported to inhibit incorporation of precursors of proteosynthesis and synthesis of nucleic acids into the P388 leukemia cells and exhibited inhibition of the RNA synthesis due probably to the biological activity of vincarubine [27]. However, vincarubine did not show any mutagenic effect when used in the SOS test [30].

Herbal medicine can serve as an alternative or a complementary medicine for treatment of cancer and use as an anti-cancer drugs. Such a treatment with herbal formulation may be fruitful as evidence has began accumulating from both animal work, cell culture study and epidemiological studies on humans indicating that herbal medicines hinder the development of cancer and prevent cancer from growth. Common cancer drugs can cause potentially unpleasant side effects. Herbal medicine is a clear alternative that has more beneficial effects on cancer patients. The availability of more specific herbal medicine should be more effective to prevent or treat cancer. Early results suggest they can do just that. But researchers hold different views on whether the herbal medicines exert this potentially beneficial effect by blocking a single enzyme or by stimulating programmed cell death by other routes. It is important to figure out the mechanism of the complex

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actions of herbal medicine that could aid the design of better formulations for chemoprevention and treatment of cancer.

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