Plant-derived natural products as leads to anti-cancer drugs

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INTRODUCTION

Today, cancer is a serious hazard to human health and affects the lives of millions of people. Cancer has become the second largest cause of death after cardiovascular diseases. A report published in 2010 by the WHO showed that the most common diagnosis were lung cancer, breast cancer and colorectal cancer, but the highest mortality rate is the lung cancer, stomach cancer and liver cancer. Globally, a lot of manpower and material resources are spent on researching and developing new drugs for prevention and treatment of cancers each year. The major obstacle to cancer treatment is the recurrence of tumor and the side effects of chemotherapy drugs.

Currently, the use of a large number of chemosynthesis of anti-cancer agents has brought great harm to the human body, and the main drawback is to suppress the immune system. Tumor cells are highly sensitive and easily induce drug resistance. Therefore, new anti-cancer drugs and therapies needs to be develop urgently.

In the 21st century, finding and developing new drugs from natural plants and marine life have attracted more and more attention (Wang et al., 2012). Various plant medicines and health products have been accepted by people from all over the world, looking forward to improving the quality of life, disease prevention and treatment of chronic diseases and geriatric diseases as well as western medicine with helpless mysterious illness. New therapeutic strategies are not only a question of eliminating cancer cells by induction of apoptosis, but also include targeting the tumor...
microenvironment, avoiding angiogenesis, modulating the immune response or the chronic inflammation which are often associated with cancers.

**DRUG DISCOVERY FROM NATURAL PRODUCTS**

Natural products have been used for centuries for the treatment of several ailments. There are many basic ancient medicinal systems derived from dietary sources. In modern society, economy and technology is more developed, traditional medicines are still used in many countries as basic healthcare. Although many conventional pharmaceutical approaches have been replaced, however there is a current resurgence in the interest in natural products by the general public, and the use of complementary and alternative medicine is increasing rapidly in developed countries. Limited research has been done, and more and more pharmaceutical industries are interested in examining their potential as sources of novel medicinal compounds (Zhang et al., 2013). Many bioactive compounds have been discovered from plants, animals and microbes, such as natural products and secondary metabolites, which have been developed into drugs to treat diseases.

Historically, natural products in the field of anti-cancer research has made significant achievements, over 60% of the clinical use of anti-cancer drugs originate from natural products (Seelinger et al., 2012), including plants, marine organisms, microbes, and more than 3,000 species of plants can be used to treat cancer. Plants have been the main resources in traditional medicine and natural products are considered as important sources of anti-tumor drugs. Potentially active ingredients are discovered mainly by chemical, biochemical, pharmacological and clinical research data screening. With the development of pharmacological experiment technology, the structure of the guide, modification and transformation of natural products have also promoted the rapid development of synthetic drugs, and with the help of modern extraction, modification and transformation, technology is bond to find some new ideas and approaches in the treatment of chronic disease.

**Natural products for cancer therapy**

Natural products derived from fruits, vegetables, herbs and marine products have served us well in combating cancer. The compounds are well characterized as possessing a wide variety of anti-tumor properties, for example, induction of apoptosis and autophagy and inhibition of cell proliferation. Active ingredients such as alkaloids, flavonoids, terpenoids, polysaccharide and saponin obtained from natural products have potent biological properties such as anti-tumor, analgesia, anti-inflammatory, immunomodulation, anti-viral, etc. activities. Marine organisms, invertebrates and algae offer rich sources of anti-cancer agents with structurally diverse bioactive compounds and bioactive secondary metabolites that possess various anti-tumor activities; indole alkaloids being the most common. A number of products were first discovered from microbes such as antibiotics, which has anti-tumor activity. The anti-tumour activity of most natural anti-neoplastic drugs often do not kill tumor cells directly, but regulates the human immune function to achieve the purpose or both. Division and duplication is a series of important events in cell cycle, and a deregulation of cell cycle can have effect on the development of cancer (Wang and Ren, 2010). DNA topoisomerase I (Topo I) is an essential enzyme involved in cell growth. The inhibition of Topo I is an important anti-cancer pathway. And also, a large number of anti-cancer drugs combat cancers through cell cycle arrest, induction of apoptosis and differentiation as well as through inhibition of cell growth and proliferation, or a combination of two or more of these mechanisms (Abubakar et al., 2012). The search for novel drugs is still a priority target for cancer therapy due to the fact that chemotherapeutic drug resistance is becoming more and more frequent.

**Alkaloid**

Alkaloids are organic compounds containing nitrogen, which have obvious biological activity and are mostly present in plants. Camptothecin (CPT) (Figure 1a) is a potent broad-spectrum anti-cancer agent that acts through inhibition of Topo I. Kuramoto et al. (2006) demonstrated (in an experiment of a 24 h oscillation mechanism of Topo I expression; to choose the most appropriate time to administer “Topo I inhibitors CPT” in tumor-bearing mice) that glucocorticoid expression are affected by 24 h variation in circulating glucocorticoid levels. Zhang et al. (2010) reported that 10-methoxy-9-nitrocamptothecin possessed potent anti-tumor activity in A549 cells in vitro and in vivo; induced cell cycle G2/M arrest in time-and dose-dependent manner of anti-cancer therapy. Matrine (Figure 1b), a major component extracted from Sophora flavescens Ait, has been demonstrated to exert anti-cancer effects in a number of cancer cells including, breast, gastric, lung, etc. It can inhibit tumor cell line MNK45, inducing apoptosis and autophagy of gastric cancer cells with a dose- and time-dependent manner (Li et al., 2013; Luo et al., 2012). The conventional treatments of acute myeloid leukemia (AML) often have severe side effects. Zhang et al. (2012) found out that matrine could inhibited proliferation and induced apoptosis in AML cell lines by influencing the
mitochondrial membrane potential; increasing the release of cytochrome C and enhancing the activation of caspase-3, etc. In animal studies, it was found that tryptanthrin inhibited the growth of human neuroblastoma cells and the proliferation of the murine myeloid leukemia WEHI-3B JCS cells in a dose- and time-dependent manner, induced neuronal differentiation of LA-N-1 cells and enhanced acetylcholine esterase activity (Liao and Leung, 2013; Chan et al., 2009). Dehydrocorydaline is isolated from Corydalis yanhusuo. Xu et al. (2012) used methods such as MTT assay, DNA ladder assay, western blotting methods to indicate that dehydrocorydaline inhibits MCF-7 cell proliferation by inducing apoptosis mediated by regulating Bax/Bcl-2, activating caspases as well as PARP; and demonstrated that dehydrocorydaline possessed anti-cancer potential on breast cancer line cells MCF-7 in vitro.

Indole alkaloid, a kind of marine alkaloid, is marine-derived secondary metabolites that widely occur amongst a variety of sources such as sponges, algae, microorganisms, etc. Studies have found that a sponge-derived bis-indole alkaloid has the anti-HIV-1 RTase and antiproliferative activity against many cancer cell lines (Bharate et al., 2012). FBA-TPQ, a marine alkaloid isolated from sponges, has the potential effect of anti-tumor on human ovarian cancer cells. In vitro and in vivo studies on anti-tumor effects have shown that FBA-YPQ could inhibit the growth of human ovarian cancer cells and proliferation; potently induce cell apoptosis and arrest G2/M cell cycle, etc (Chen et al., 2011).

**Taxane and podophyllotoxin**

Tacane and podophyllotoxin have potent anti-tumor activities but their poor cytotoxic selectivity, serious side
effects and limited effectiveness are the main problems in using them in anti-cancer therapy (Chen et al., 2013). Paclitaxel (Taxol, Figure 1c) and docetaxel (Taxotere, Figure 1d) are very important anti-cancer drugs that have exhibited some anti-cancer activity against several malignancies including lung cancer, breast and ovarian cancer, prostate cancer, etc. Paclitaxel possess microtubule function leading to block mitosis and formation of polyploidy giant cancer cells (Zhang et al., 2013). Clinical effect of taxane injection is significant but is also associated with severe toxicities. The technology of albumin-bound paclitaxel is utilizing albumin to deliver paclitaxel, which can increase the tumor uptake and response rate, and improve the tolerability (Yardley, 2013).

Podophyllotoxin (Figure 2e) inhibits the polymerization of tubulin and develop diverse derivatives of podophyllotoxin, such as, etoposide, etopophos and teniposide, which have been developed and are currently use in clinics for treatment of a variety of malignancies and in combination with other drugs. Deoxy-podophyllotoxin and lignans-podophyllotoxin from Podophyllum hexandrum are secondary metabolites with potential cancer therapy. But the supply of natural source is becoming increasingly problematic, which calls for the need for urgent alternative sources. Various plant selection methods and criteria were designed and applied in order to select alternative sources of podophyllotoxin lignan analogues. Renouard et al. (2011) developed and validated an efficient extraction protocol for podophyllotoxin and deoxypodophyllotoxin from Juniperus species and applied it to 13 Juniperus species as an alternative source of the metabolites. Zhao et al. (2013) found out that the HY-1 of podophyllotoxin derivatives function as multi-targeted DNA topoisomerase II inhibitor; as anti-cancer cells proliferation and; induced

Figure 2. Chemical structures of podophyllotoxin (e), licochalconeA (f), baicalin (g) and isoflavones (h).
G2/M phase arrest in human colon cancer cells.

Flavonoids

Flavonoids include isoflavones, flavonols, flavones, anthocyanidins, catechins, flavanones, etc. Studies have shown that flavonoids have anti-cancer effects.

Licorice is a common Chinese medicinal herb and studies conducted showed that liquiritigenin- the flavonoid compound in licorice- can effectively inhibit the proliferation of human cervical carcinoma cell of tumors xenografts in nude mice (Liu et al., 2012).

LicochalconeA (Figure 2f) also has effects against gastric cancer. It inhibits cell cycle and induces cell apoptosis in cancerous cells (Xiao et al., 2011).

Glabridin has inhibitive effect in human breast cancer. It inhibits cell metastasis, decrease tumor angiogenesis and inhibits invasion of MDA-MB-231 cells (Hsu et al., 2011).

Baicalin (Figure 2g) possesses anti-inflammatory, antioxidant and anti-tumor properties. In the study of human hepatocellular carcinoma (HCC), Zhang et al. (2012) found out that baicalin could induce autophagic cell death by down-regulating CD147 in SMMC-7721 cell line. Combination treatment of baicalin and baicalein had synergistic effect of anti-proliferation, enhanced apoptosis and reduced the level of bcl-2 expression. For example, baicalin and baicalein significantly inhibited the viability of ovarian cancer cells. Both of them could inhibit cancer cell viability and expression of cell factors (Zhou et al., 2009; Chen et al., 2013).

Isoflavones (Figure 2h) mainly exists in leguminous plants, with a similar structure to estrogen, including soy isoflavones, genegonflavones, etc. Phenoxodiol, a novel isoflavone derivative, has been shown to induce apoptosis both in vitro and in vivo, even in chemoresistant cancer cells (Alvero et al., 2008).

Quercetin is a plant-derived flavonoid that can inhibit growth and induction apoptosis in several types of tumor cells, such as, human cervical cancer, prostate cancer, epidermal growth factor receptor-overexpressing oral cancer, osteosarcoma, etc.

Resveratrol and quercetin in combination inhibited growth in human CLL cells through cytotoxic, cytostatic and apoptotic effects, and also have effect on HT-29 colon cancer cells (Gokbulut et al., 2013; Del Follo-Martinez et al., 2013).

Propolis contains a variety of compounds. Caffeic acid phenethyl ester (CAPE) is a strong bioactive component extracted from propolis. Modern pharmacological research has proved that CAPE can suppress human pancreatic cancer cell proliferation, can adjuvant treatment of human oral squamous cell carcinoma, inhibit the growth of cancer cells and Akt signaling in human prostate cancer cells, and as well have effect on cervical cancer cells (Chen et al., 2013; Kuo et al., 2013; Lin et al., 2013; Hsu et al., 2013). Many other flavonoids such as rutin, epigallocatechin, silymarin, also have anti-cancer activity and special molecular mechanisms are being studied.

Saponins

Variety of saponins with complex structure widely exists in plants. Saponins have been reported to possess various biological properties such as anti-cancer and anti-inflammatory activity. The most widely studied is the ginsenoside.

Ginsenoside is a kind of triterpenoid saponins, and it is the main active ingredients in ginseng. A large number of studies have shown that ginsenoside has higher anti-tumor activity, non-toxic side effects on normal cells and has a synergistic effect with other chemotherapy drugs such as cisplatin. Ginsenoside regulates the proliferation of tumor cells, inducing differentiation and apoptosis of cells to exert anti-tumor effects.

Rg3 (Figure 3i) and Rh2 (Figure 3j) are the most studied and the most relevant anti-tumor components. Studies have proven that Rg3 can promote TRAIL (Tumor Necrotic Apoptosis Inducing Ligand) by inducing apoptosis of hepatocellular carcinoma cell line. However not in normal hepatocytes, and can be used as a chemo-sensitizer for the treatment of cancer, and also have effect on glioma and on other cancers (Lee et al., 2013). Ginsenoside Rh2 can treat leukemia by blocking the cell cycle; treat pancreatic cancer by inhibiting proliferation, migration, invasion and inducing apoptosis of cancer cells (Tang et al., 2008).

Ginsenoside Rk1 has the biological activity of anti-tumor activity in human hepatocellular carcinoma HepG2 cells in vitro. RK1 markedly inhibited telomerasc activity and cell growth along with significant morphological change and induced apoptosis (Kim et al., 2008).

Ginsenoside derivatives in anti-cancer activity are also very strong. PPD, the metabolites of Rg3, inhibited prostate cancer cell growth and proliferation, induced apoptosis which leads to an arrest in the G1 phase of the cell cycle. Therefore it could function as a potential therapeutic agent in treatment of prostate cancer and it also has stronger effects on colon cancer (Wang et al., 2008; Gao et al., 2013). Ginsenoside metabolite compound K can inhibit a variety of cancer cells growth. It can improve the results of treatment of pediatric acute myeloid leukemia and animal experiments have shown that compound K may also have the effect of prevention and treatment of colon cancer (Chen et al., 2013; Zhang et al., 2013). Yun et al. (2013) found out that ginsenoside derivative Rp1 has the effect of multiple drug resistance. Many other saponins have anti-cancer activity.

Tuberoside-1(TBMS1) is isolated from the Bolostemma paniculatum, can inhibit BGC832 gastric
cancer cell proliferation (Zhang et al., 2013).
Platycodin isolated from Platycodon grandiflorum, can induce apoptosis in prostate cancer cells (Lee et al., 2013).
PE, a new sulfated saponin from sea cucumber that have anti-angiogenic activity associated with inhibition of VEGFR2 signaling, anti-tumor activity associated with decreased proliferation of tumor cells and increased apoptosis of both endothelial in mouse sarcoma 180 and hepatoma 22 models (Tian et al., 2005).
Asterosaponin 1 is a natural product found in marine organisms that could significantly suppressed U87MG cell proliferation and may play a critical role in anti-tumor therapy (Cheng et al., 2006).

**Polysaccharide**

Polysaccharide (Figure 3k) play anti-tumor role by a variety of approaches and level of participation and regulation in the immune system, such as regulating phagocytic function of the reticulo-endothelial system, improve the natural killer (NK) cell activity, activate macrophages, induce the expression of immune-regulatory factors, affect cell metabolism, inhibit tumor cell cycle, inhibit the activity of SOD in tumor tissues, etc. Higher relative molecular mass of the neutral polysaccharide can improve the function of macrophage in vivo, acidic polysaccharide can promote tumor necrosis factor release, directly killing and inhibiting tumor cells. The polysaccharide derived from Prunella vulgaris has been proven to have anti-HSV activities by inhibiting the virus binding and penetration into host cells (Zhang et al., 2007).

Astragalus polysaccharides (APS) are the active ingredients in Astragalus membranaceus. When used alone, the APS had no anti-tumor activity on tumor cells in vitro. However, it can be combined with other anti-

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*Figure 3. Chemical structures of ginsenoside Rg3 (i), Rh2 (j), and polysaccharide (k).*
cancer drugs to increase the cytotoxicity of certain chemotherapy drugs in H22/ADM cells and enhance the chemo-sensitivity of the cells (Tian et al., 2012). \textit{Ganoderma lucidum} have been used to prevent and treat various human diseases. Data obtained from previous research have showed that \textit{G. lucidum} polysaccharide (GLPS) could suppress tumorigenesis or inhibit the growth of tumor by direct cytotoxic effects and anti-angiogenic actions. It can mediate immunomodulation and affect immune cells and; immune-related cells (Xu et al., 2011).

\textit{In vitro} studies of chito-oligosaccharides (COS) significantly inhibited human hepatocellular carcinoma (HepG2) cell proliferation; reduced the percentage of S-phase and decreased DNA synthesis rate in COS-treated HepG2 cells. \textit{In vivo}, COS inhibited the growth of tumor of HepG2 xenografts in severe combined immune-deficient (SCID) mice (Shen et al., 2009). The study showed a potential anti-tumor growth and anti-metastatic effect of COS in cancer treatment. There are many other polysaccharides with anti-tumor activity such as safflower polysaccharide (SPS), fucoidan, tremella polysaccharide, etc.

\textbf{Others}

There are many other kinds of anti-cancer activity of natural products.

Andrographolide (Andro), a natural diterpenoid lactone isolated from \textit{Andrographis paniculata}, has been shown to inhibit breast cancer cell proliferation, migration and arrest cell cycle at G2/M phase; and also induce apoptosis through caspase independent pathway. It can act as an effective anti-tumor and anti-angiogenic agent for the treatment of breast cancer (Kumar et al., 2012).

Sesquiterpene lactones (SL) are plant secondary metabolites; test two SL molecules, 3-β-methoxy-isosceo-tanapartholide (β-tan) and salograviolide A (Sal A) of their anti-tumor activity have shown that they could selectively inhibit growth of tumor promoter-induced cell and transformation of JB6P+ cells at concentrations (Saikali et al., 2012).

27-kDa trichosanthin (TCS) is a ribosome inactivating protein found in Chinese herbal plant: \textit{Trichosanthes kirilowii maximowicz} (TianHua Fen), has anti-proliferative and apoptosis-inducing activities in both estrogen-dependent human MCF-7 cells and estrogen-independent MDA-MB-231 cells, and significantly reduce tumor volume and weight (Fang et al., 2012). Zhao et al. (2012) have found a polysaccharide-protein complex from \textit{Scolopendra subspinipes mutilans} L. Koch, which can inhibit tumor growth \textit{in vivo} by improving anti-tumor immune response and down-regulating AA-metabolic pathway. Polymeric black tea polyphenols (PBPs) have been shown to possess the anti-tumor-promoting effect in two-stage skin carcinogenesis (Kumar et al., 2012). A new alkaloid CS-1 have been extracted from traditional Chinese medicine that can probably inhibit the epidermal growth factor binding to its receptor; influence the transcription of cyclin D1 cell cycle arrest in G1/S phase, so as to inhibit the proliferation of several human cancer cells (Du et al., 2012).

Doxycycline may exert its anti-tumor effects through inhibition of FAK signaling pathway (Sun et al., 2009). Naringenin can enhance the anti-tumor effect of doxorubicin by selectively modulating drug efflux pathways better than using doxorubicin alone, and can be developed as a adjuvant drug in the treatment of human cancers (Zhang et al., 2009). These N-alkylthiolated beta-lactam analogues can be used as potential anti-cancer drugs; Frezza et al. (2008) discovered that beta-lactams have DNA-damaging and apoptosis-inducing activity in various tumor cell lines, and can inhibit the growth of mice bearing breast cancer xenografts associated with induction of DNA damage and apoptosis in tumor tissues.

\textbf{Technologies for natural-product improvement of anti-cancer}

Even though conventional anti-carcinogen play an important role in the treatment of most solid tumors, there are limitations in the use of single chemotherapeutic drug as anti-tumor treatment agent; such as, emergence of drug resistance, high cell toxicity and limited regime of clinical uses (Zhang et al., 2014; Zhang et al., 2013). Therefore, there is need for new therapeutic strategy, for example, to improve the efficacy of natural compounds, to combine with chemical drugs and reduce toxicity as well as side effects; increase selectivity and reduce the risk of using chemical medicine alone. This can not only improve treatment efficiency but also overcome the limitations of cell toxicity and adverse reactions. In seeking a new therapeutic strategy, this comprehensive therapy is a promising way that can effectively target multifactorial diseases (Wang et al., 2013).

In clinical applications, CPT has the side effects of poor drug solubility, instability of the active form \textit{in vivo} and cell toxicity. A polymeric nano-particle that comprise of cyclodextrin-poly (ethylene glycol) copolymer (CDP) conjugated to CPT (CRLX101) could address these issues. In the CRLX101 preclinical and clinical data, CDP can address not only solubility, formulation, toxicity and pharmacokinetic challenges associated with administration of CPT, but also can impart unique biological properties that enhance pharmacodynamics and efficacy of CPT (Svenson et al., 2011). Paclitaxel has very strong anti-tumor effect, but serious side effects including hypersensitivity reactions, drug resistance and other cell toxicity limit its clinical application. In order to make better use of PTX, modifying structure or
Chemotherapy combined with anti-tumor drugs could improve the dilemma. Research has proven that a novel compound, paclitaxel solid dispersion (PSD), a cremophor-free, could increase the safety and efficacy of paclitaxel (Liu et al., 2012). Lipid nano-emulsions (LDE) can be used as drug carriers of paclitaxel (PTX) and etoposide (ETP). LDE-PTX+ETP drug-targeting therapy combination have the obvious anti-cancer properties and reduced the toxicity in melanoma-bearing mice compared to PTX+ETP (Kretzer et al., 2012). The GM-CSF-surface-modified tumor-cell vaccine may have potential clinical benefit for patients with prostate cancer when it is combined with paclitaxel (He et al., 2011). Effective use of docetaxel maintenance chemotherapy after paclitaxel and carboplatin combination chemotherapy in patients with advanced ovarian cancer is much better than a single kind of medicine (Isonishi et al., 2013). PEGylated PLGA-based nano-particles grafted with peptide or peptidomimetic can have direct action on tumor endothelium and enhance the anti-tumor efficacy of PTX (Danhier et al., 2009). The flavonoid-metal complexes can obviously enhance activity of antibacterial, antiviral, anti-inflammatory, anti-tumor and anti-free-radical. Genistein, a soybean isoflavone derivative, combined with cisplatin, can enhance the inhibitory activity on proliferation of hepatocellular carcinoma (HCC) cells; decrease the rate of recurrence and metastasis on tumor cells after hepatic resection (Chen et al., 2013). Rg3 combined with cisplatin has synergistic anti-cancer effect and can inhibit nephrotoxicity and cytotoxicity induced by cisplatin (Lee et al., 2012). The effect of Rg3 combined with docetaxel in the treatment of prostate cancer is better than the use of single drug (Kim et al., 2010). Furthermore, the combination of immunotherapy and chemotherapy was significantly efficacious than either of them alone. It could thoroughly stimulate the immune effects and enhance the anti-tumor function of chemotherapeutical drugs, and can also enhance the cytotoxicity and reduce some resistance mechanisms by modifying the structures of natural product compounds.

CONCLUSION

The advent has led to a booming of looking for anti-cancer drugs from natural products, where people began to pay attention to the herbal ingredients. In addition to looking for high selectivity, strong activity, low side effects and a wide range of anti-tumour drugs from natural resources, people also began to focus on cancer prevention research. Compounds extracted from natural resources can enhance immune cells or body immunity, anti-tumor effects and inhibit the proliferation of cancer cells. Not just biologically toxic compounds have attracted people’s attention but also more non-toxic ingredients that have health care effects. Disease prevention is more important than treatment, so is cancer. With the progress of science and technology, people now have deep understanding of tumor, making the prevention of cancer possible. The development of cancer prevention and health care products from natural products has a broader prospect, greater economic and social benefits when compared with anti-cancer drugs.

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