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REVIEW ARTICLE

Plant-derived natural products as leads to antitumor drugs

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Abstract

Cancer is the main cause of death worldwide. Chemotherapeutic agents used for disease treatments have shown limited antitumor activity, with a high recurrence rate. It has prompted the research efforts to identify anti-tumor compounds. Research on medicinal plants began to focus on discovery of natural products as potential leads to antitumor drugs. Medicinal plants are very interesting, have the ability to produce remarkable chemical structures with diverse biological activities. Plant-derived natural products have been used by human societies for millennia, and their biological source is most likely available and can be employed for production, have been considered as valuable sources for antitumor drugs. Many interesting natural products with biological activity are evidenced in the past few years. This review highlights the potential of natural compounds as candidates for antitumor drugs. A brief illustration of the sources and general biological effects of the main classes of plant-derived natural compounds and related molecules are also provided.

Keywords: Natural products; antitumor; cancer; secondary metabolites; drug discovery.

1. Introduction

Malignancy is serious disease condition which endangers people's lives and health (Hakimzadeh, Ghazanfari, Rahmati, & Naderimanesh, 2010). Throughout medical history, plants have been main resources in traditional medicine and natural products are considered as important sources for antitumor drugs (Zhang *et al*., 2010; Wang *et al*., 2012). With the intensive need for the development of more effective and safer agents for chemoprevention and therapy of human tumor, natural products from plants have been expected to play significant roles in creating new and better chemopreventive and therapeutic agents (Mans, da Rocha, & Schwartsmann, 2000). In general, conventional therapies cause serious side effects and, at best, merely extend the patient's lifespan by a few years. Chemotherapeutic agents have shown limited antitumor activity, with a high recurrence rate. It has prompted major research efforts to identify novel anti-tumor compounds and the need to use alternative concepts or natural approaches to the prevention of tumor (Reddy, Odhav, & Bhoola, 2003; Amin, Kucuk, Khuri, & Shin, 2009; Robles-Fernández, 2012). Plant secondary metabolites as natural products can act as potent antitumor agents.

The tumor preventive or protective activities of the various natural products lie in their effects on cellular defences or by targeting the key transcription factors like nuclear factor kappa B, activator protein, signal transducers and activators of transcription and others (Butler, 2008; Pan, Ghai, & Ho, 2008; Aravindaram, & Yang, 2010; Tosetti, Noonan, & Albini, 2009). The differential effects of natural products from plants in tumor cells may be due to different abilities to induce specific apoptotic pathways, modify the levels of major metabolic enzymes, or induce detoxifying enzymes and tumor suppressor genes (Shammas *et al*., 2006; Kwon, Barve, Yu, Huang, & Kong, 2007; Singh *et al*., 2008). This review will focus on anti-tumor research, and provide insights into the value of natural products for therapeutic areas.

2. Benefits of natural products

The plants have been main resources in traditional

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medicine and natural products are considered as important sources of antitumor drugs. Natural products have no side effect to most of the normal cells in treatment of tumor, and mixtures of natural products extracts can have combination effects on tumor cell growth. The natural products are expected to play significant roles in creating new and better chemopreventive and therapeutic agents. The reported health benefits of natural product include antioxidant, antitumor, antimutagenic, and immunomodulatory activities. Many of the beneficial effects are related to the presence of alkaloid, diterpenoid, triterpenoid, polysaccharide, polyphenols and flavonoids. Many studies have explored the effects of the natural product in tumor, and various mechanisms have been proposed as to how these different extracts help in inhibiting tumor growth.

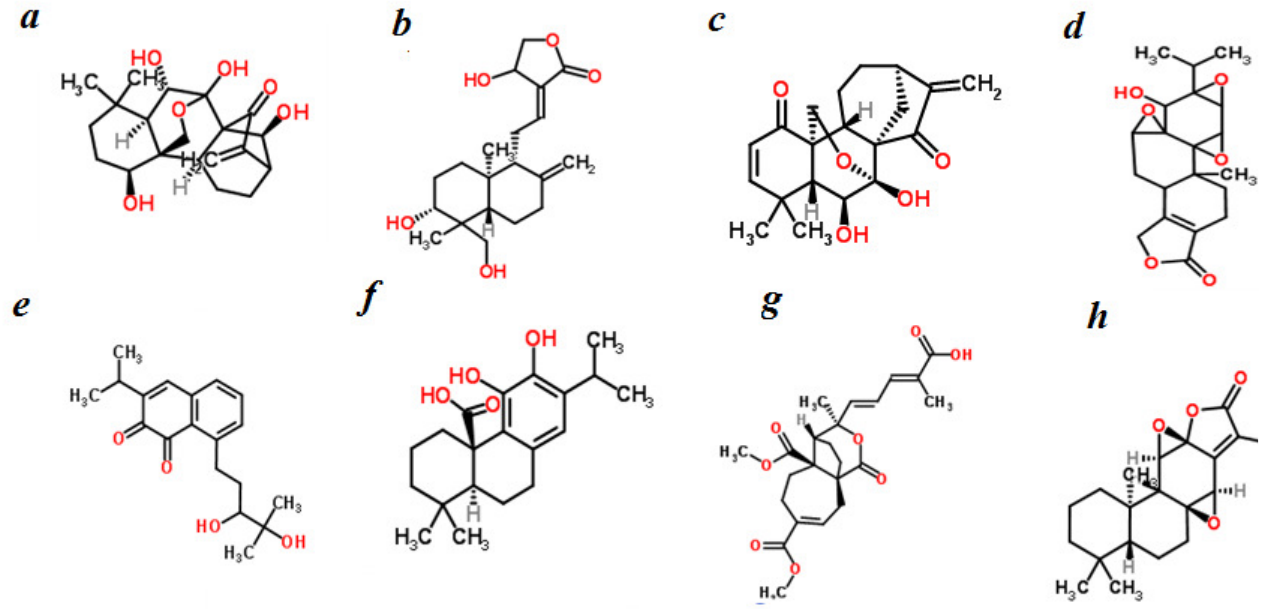

Fig. 2. Chemical structure of diterpenoid. a, oridonin; b,andrographolide; c, eriocalyxin B; d, triptolide; e, salvicine; f, carnosic acid; g, pseudolaric acid B; h, jolkinolide B

3. Natural products for tumor treatment

3.1. Alkaloid

3.1.1. Evodiamine

Evodiamine (Fig. 1a) is a quinazolinocarboline alkaloid isolated from the fruits of *Evodiae fructus*. It is an effective natural compound for the treatment of gastric cancer. Dong *et al*. (2012) had identified a number of evodiamine derivatives that showed substantial increase of the antitumor activity, with GI(50) values lower than 3 nM. It also showed good *in vivo* antitumor efficacy and low toxicity (Rasul *et al*., 2012). It may represent a candidate for *in vivo* studies of monotherapies or combined antitumor therapies (Chao *et al*., 2011).

3.1.2. Neferine

Neferine (Fig. 1b), a major alkaloid component in lotus embryos, has an effect on human osteosarcoma cells (Zhang *et al*., 2012). Simultaneously, mitochondrial-mediated ROS generation induced by neferine leads to caspase-dependent apoptosis in HepG2 cells (Poornima, Quency, & Padma, 2013). Result showed a direct antitumor effect, suggesting that consumption of neferine may have tumor-preventive and tumor- therapeutic benefit.

3.1.3. β-carboline alkaloid

β-carboline (Fig. 1c) alkaloids are a large group of natural indole alkaloids with different degrees of aromaticity, some of which are widely distributed in nature (Cao, Peng, & Wang, 2007). From *Trigonostemon lii* Y.T. Chang study was conducted to give six new β-carboline alkaloids, trigonostemines A-F and eight known β-carboline alkaloids. All of them were evaluated for their cytotoxic activities against human cancer cell lines. Trigonostemines A and B exhibited stronger inhibitory activities (Li *et al*., 2012). Recently, researchers have demonstrated that harmol, a β-carboline alkaloid, induced autophagy and cell death in human NSCLC A549 cells (Abe, Yamada, Moriya, & Miyazawa, 2011).

Furthermore, β-carboline significantly suppressed the growth and cell cycle progression of the human LNCaP prostate cancer cell line (Bemis, Capodice, Gorroochurn, Katz, & Buttyan, 2006).

3.1.4. Tetrandrine

Tetrandrine (Fig. 1d), a bisbenzylisoquinoline alkaloid isolated from the *Stephaniae tetrandrae*, and exhibits potent antitumor effects. It is a highly lipid-soluble and hydrophobic molecule with a low molecular weight, and may cross the blood brain barrier. Thus, it could be used for the treatment of intracerebral gliomas (Chen & Tseng, 2010). Tetrandrine exerts an antitumor effect on cultured and subcutaneous CT-26 cells in concentration- and time-dependent manner (Wu, Chen, Chen, Lin, & Tseng, 2010). Previously reported that high concentrations of tetrandrine induce apoptosis in liver cancer cells (Liu, Gong, Mao, & Li, 2011). Gong *et al*. (2012) had studied that tetrandrine is a potent autophagy agonist and may be a promising clinical tumor chemotherapeutic agent.

3.1.5. Others

Wang, Chen, & Wang (2010) isolated six new bisbenzylisoquinoline alkaloids, racemosidines A-C and racemosinines A-C, and four known compounds from the roots of *Cyclea racemosa*. The study suggested racemosidines A-C exhibited significant cytotoxicity against HCT-8 and BEL-7402 tumor cells, and racemosidines A (Fig. 1d) was also cytotoxic against A2780 tumor cells.

3.2. Diterpenoid

3.2.1. Oridonin

Oridonin (Fig. 2a), an ent-kaurane diterpene isolated from Chinese medicinal plant *Isodon rubescens*, has been shown to have multiple biological activities. Among them, the antitumor activity has been repeatedly reported, and was related to its ability to interfere with several pathways such as cell proliferation, cell cycle arrest, apoptosis and/or autophagy (Dal Piaz *et al*., 2013). However, low solubility has limited its clinical applications. It was found that oridonin nanosuspension was more effective than free oridonin on G2/M cell cycle arrest and apoptosis in the human pancreatic cancer PANC-1 cell line (Lou *et al*., 2009; Qi *et al*., 2012). Moreover, the study confirmed the inhibitory effects of oridonin on colorectal cancer. The down regulation of AP-1 might be an initial response to treatment by oridonin. In turn, this regulation could affect the expression of the NF-κB and mitogen-activated protein kinase pathways, thereby inhibiting tumor growth (Gao *et al*., 2010; Jin, Tan, Liu, & Ding, 2011). Furthermore, oridonin can cause the suppression of proliferation in C6 astrocytoma cells and the cell death induced by oridonin (Yin, Sheng, Lin, Zhou, & Zhang, 2012), and it induced autophagy in prostate cancer PC-3 cells. The growth of PC-3 cells was inhibited, and autophagy was also induced by oridonin (Ye *et al*., 2012).

3.2.2. Andrographolide

Andrographolide (Fig. 2b) is the major active principle of *Andrographis paniculata* which is a diterpenoid lactone (Sabu, Padmesh & Seeni, 2001). Andrographolide has caused ROS-dependent apoptosis in lymphoma cell lines and in primary tumor samples, which was enhanced by depletion of GSH and inhibited by NAC or the pan-caspase inhibitor Z-VAD-FMK (Yang *et al*., 2010). The andrographolide was shown to inhibit breast cancer cell proliferation, migration and arrest cell cycle at G2/M phase and induces apoptosis through caspase independent pathway and least side effects (Menon & Bhat, 2010; Kumar *et al*., 2012). It could be a promising anti-cancer agent in combination therapy *via* its potent inhibitory effect on autophagy by disrupting autophagosome-lysosome fusion (Zhou *et al*., 2012).

3.2.3. Eriocalyxin B

Eriocalyxin B (EriB) (Fig. 2c) is a natural diterpenoid purified from *Isodon eriocalyx*. In murine xenograft lymphoma models, it significantly inhibited lymphoma cell proliferation and induced apoptosis in association with caspase activation (Zhang *et al*., 2010). Without affecting normal hematopoietic progenitor cells proliferation, EriB might be a potential treatment for leukemia by targeting AML1-ETO oncoprotein and activating apoptosis pathways (Wang *et al*., 2007). Liang *et al*. (2012) isolated three new ENT-kaurane diterpenoids, glaucocalyxin H, glaucocalyxin I, and glaucocalyxin J, together with four known diterpenoids, from the leaves of *Isodon japonica* Hara var. *glaucocalyx* (Maxim.). Glaucocalyxin H showed potent inhibitory activities against tumor cell lines and diterpenoids exhibited significant selective cytotoxicity on seven tumor cell lines. Deng *et al*. (2009) had purified ExcisaninA, a diterpenoid compound from Isodon MacrocalyxinD. It showed ExcisaninA could inhibit the proliferation of Hep3B and MDA-MB-453 cells *via* induction of apoptosis.

3.2.4 Triptolide

Tripterygium wilfordii Hook. F. is a Chinese medicinal herb which has been used widely and successfully for centuries in treating inflammatory diseases (Liu, Ma, & Zhou, 2011). Triptolide (TPL, Fig. 2d) is a diterpenoid triepoxide purified from *Tripterygium wilfordii* Hook F, is a potential therapeutic agent that effectively induces apoptosis in a wide variety of cancer cells. TPL inhibited the proliferation and induced the apoptosis of pancreatic cancer cells *via* the downregulation of DcR3 expression (Phillips *et al*., 2007; Wang *et al*., 2012). Chen *et al*. (2009) suggested TPL induces prominent growth inhibition and apoptosis in two oral cancer cell lines, SCC25 and OEC-M1 and in KB cells. Triptolide not only inhibits tumor growth

but also induces apoptosis of these drug-resistant tumor cells in xenograft mouse models. Moreover, triptolide combined with 5-fluorouracil could be an alternative strategy for chemotherapy enhancement (Chen *et al*., 2010).

3.2.5. Salvicine

Salvicine (SAL, Fig. 2e), a novel diterpenoid quinone compound, exhibits potent antitumor activities both *in vitro* and *in vivo* by poisoning topoisomerase II (Topo II) and has entered Phase II clinical trials for cancer therapy (Cai *et al*., 2008). It has indicated that salvicine-elicited ROS plays a central role in salvicine-induced cellular response including Topo II inhibition, DNA damage, circumventing MDR and tumor cell adhesion inhibition (Meng & Ding, 2007). Salvicine was also found to have a profound cytotoxic effect on multidrug-resistant (MDR) cell lines by down-regulating the expression of MDR-1 mRNA of MDR cells (Meng, Zhang, & Ding, 2001). In addition, Qing *et al*. (2001) showed that salvicine is capable of inhibiting cell proliferation and induce characteristic changes of apoptosis in both human leukemia K-562 and gastric carcinoma SGC-7901 cells.

3.2.6 Other diterpenoids

Carnosic acid (Fig. 2f) isolated from the plant Rosemary, on androgen-independent human prostate cancer PC-3 cells. Carnosic acid may have the potential for use in the prevention and/or treatment of prostate cancer (Kar, Palit, Ball, & Das, 2012). Pseudolaric acid B (Fig. 2g) was isolated from *Pseudolarix kaempferi* Gordon. It induced apoptosis through p53-dependent pathway in human gastric carcinoma cells, may be a novel promising agent for treating human gastric carcinoma (Meng & Jiang, 2009). In addition, chemical investigation into the twigs and leaves of *Sapium insigne* afforded sapinsignoids, and sapinsignoids exhibited significant cytotoxicity against the A-549 tumor cell line, while sapinsignoids showed moderate cytotoxicity against the HL-60 cell line (Liu *et al*., 2012). Molecular mechanisms of jolkinolide B (JB, Fig. 2h) from the root of *Euphorbia fischeriana* Steud were explored. JB-induced apoptosis of MCF-7human breast tumor cells occurs through the PI3K/Akt/mTOR signaling pathway (Xu, Chen, Hou, Du, & Liu, 2013). The antitumor effects of five phenolic diterpenes derived from *Hyptis incana* were examined on neuroblastoma cells. It showed phenolic diterpenes isolated from *Hyptis incana* have multiple antitumor effects on neuroblastoma cells (Tabata *et al*., 2012).

3.3. Triterpenoid

3.3.1. Ursolic acid

Ursolic acid (Fig. 3a) is a pentacyclic triterpenoid derived from leaves, berries, fruits, and flowers of medicinal plants. Ursolic acid has been shown to inhibit tumorigenesis and suppress angiogenesis, it may elicit its strong antitumor effects *via* upregulation of the PTEN gene and inhibition of the PI3K/Akt pathway (Wu *et al*., 2012). Kim *et al*. (2011) had found that ursolic acid induce apoptosis through both mitochondrial death pathway and extrinsic death receptor dependent pathway in human breast cancer cell line. It indicated that ursolic acid could be used as a potential anticancer drug for breast cancer. Additionally, the radiosensitizing effects of ursolic acid (UA). Ionizing radiation (IR) -induced apoptosis in tumor cell lines was significantly enhanced by ursolic acid, as reflected by DNA fragmentation, cellular redox status, mitochondrial dysfunction and modulation of apoptotic marker proteins. Ursolic acid combined with IR was also effective for inhibiting tumorigenesis in B16F10 melanoma cells implanted into mice (Koh *et al*., 2012).

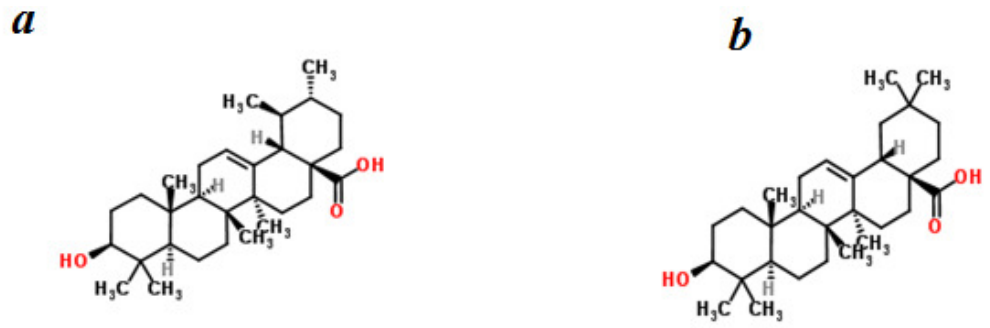

Fig. 3. Chemical structure of triterpenoid. a, ursolic acid; b, oleanolic acid

3.3.2. Oleanolic acid

Oleanolic acid (OA) (Fig. 3b) is a naturally occurring triterpenoid exhibits potent anti-tumor activity against many tumor cell lines in food materials. OA induces

apoptosis by altering cellular morphology as well as DNA integrity in HaCaT cells, with comparatively low cytotoxicity (George, Kumar, Suresh, & Kumar, 2012). It is a promising agent for treatment of osteosarcoma and mTOR signaling may contribute to its anti-tumor effects on osteosarcoma cells (Zhou *et al*., 2011). Likewise, OA stimulates NO and TNF-alpha release and is able to upregulate iNOS and TNF-alpha expression through NF-kappaB transactivation, which also may be the mechanism underlying its antitumorigenic effects (Choi, You, & Jeong, 2001).

3.3.3. Other triterpenoids

Limonoids are triterpenoids found in citrus, and possess tumor preventive properties *in vitro* and *in vivo* assays, that suggested inhibition of cell proliferation by methyl nomilinate occurs due to G1 cell cycle arrest (Kim, Jayaprakasha, Vikram, & Patil, 2012). There are eight triterpenoids isolated from the aerial parts of *Thalictrum fortunei*, the growth inhibitory effects of on tumor cell lines, probably through the P53 protein-induced apoptosis pathway (Zhang *et al*., 2011). A novel triterpenoid from the leaves of *Sinojackia sarcocarpa*, was isolated, and has a significant antitumor activity both *in vitro* and *in vivo* (Wang *et al*., 2011). Five triterpenoid saponins were isolated from *Anemone flaccida* Fr. Schmidt. The inhibitory effects of saponins on proliferation of HeLa cells have been studied, the data presented indicated that naturally occurring triterpenoid saponins can be regarded as excellent structures for the potential development of new antitumor agents (Han, Li, Huang, Yu, & Fang, 2009). The apple total triterpenoid content (ATT) was extracted and concentrated from apple peels. *In vitro*, ATT showed potent antiproliferative activities against human breast cancer, human colon cancer, and human liver cancer cell lines. *In vivo* antitumor experiments showed that ATT could substantially reduce the occurrence and growth of mammary tumor in a rat model (He, Wang, Hu, & Zhang, 2012). Tubeimoside-1 a triterpenoid saponin also induces apoptosis of HepG2 cells extracted from the traditional Chinese herb *Bolbostemma paniculatum* (Maxim.) Franquet (Cucurbitaceae) (Yin *et al*., 2011). Twenty triterpenoid saponins from *Ardisia japonica* were evaluated for their anti-proliferative activity on human liver cancer cells and normal liver cells. Eight saponins selectively inhibited the growth of liver cancer Bel-7402 and HepG-2 cells without affecting the survival of normal liver HL-7702 cells (Li *et al*., 2012). Two new triterpene saponins, mandshunosides A and B, isolated from the roots and rhizomes of *Clematis mandshurica* also showed inhibitory activities against two colorectal human cancer cells HCT 116 and HT-29 (He, Li, Zhang, & Liu, 2011). A combined treatment with conventional chemotherapies can enhance the effectiveness of chemotherapeutic agents against tumors. The triterpenoid, pristimerin, synergistically enhances taxol response of cervical cancer cells through DR5 expression and Bax activation (Eum *et al*., 2011).

3.4. Flavonoid

3.4.1. Baicalein

Baicalein (Fig. 4a), a flavone present in *Scutellaria baicalensis* Georgi, has been demonstrated to possess antitumor activity in a variety of cancer cells *in vitro*. Baicalein exhibited most potent inhibitory effect on proliferation and migration on the analyzed tumor cell line (Lalou *et al*., 2013), and baicalein significantly inhibits growth and induces apoptosis in ESCC cells *in vitro* (Zhang, Lu, Guo, Zhang, & Meng, 2013), and induced apoptosis *via* Akt activation in a p53-dependent manner in the HT-29 colon cancer cells and that it may serve as a chemopreventive or therapeutic agent for HT-29 colon cancer (Kim *et al*., 2012). Moreover, Li *et al*. (2012) had demonstrated that baicalein repressed growth inhibition and induced apoptosis and activation of caspase-9 and caspase-3 in T24 bladder cancer cells, which indicated that baicalein may be an effective agent in the clinical management of bladder cancer.

3.4.2. Mixture of flavonoids

Pinus massoniana bark extract (PMBE), a mixture of flavonoids, showed capability of inducing cell apoptosis. It inhibits the tumor cell growth by inducing cell apoptosis and improving lymphoproliferation (Zhang *et al*., 2012). It selectively induces apoptosis in HepG2 human hepatoma cells through caspase-dependent pathways without impact on normal liver L-02 cells, and exerted dose-and time-dependent inhibition on tumor growth *in vivo*, making it a potential candidate for anticancer therapeutics (Ma *et al*., 2010).

3.4.3. Baohuoside

Baohuoside-I (Fig. 4b), a flavonoid extracted from a Chinese medicinal plant, exhibits anticancer activity. It might exert its apoptosis-inducing cytotoxic effect *via* the ROS/MAPK pathway (Song *et al*., 2012). Baohuoside-I significantly inhibited Eca109 human esophageal squamous carcinoma cell proliferation and induced Eca109 cell apoptosis, and caused a dose-and time-dependent inhibition of cell growth and an induction of apoptosis *in vitro* and *in vivo* (Wang *et al*., 2011).

3.4.4. Prenylated isoflavonoids

The major constituents from the fruits of *Maclura pomifera* are the prenylated isoflavones, osajin (Fig. 4c) and pomiferin (Fig. 4d). Osajin showed antitumor activity in different tumor cell lines, and found to significantly induce apoptosis of nasopharyngeal carcinoma cells in a dose-and time-dependent manner. Osajin could be developed as a new effective and chemopreventive compound for human nasopharyngeal carcinoma (Huang

et al., 2011). Pomiferin exhibited growth inhibitory activity on five human tumor cell lines and more sensitive inhibitory activity on the HCT-15 colon tumor cell line (Son *et al*., 2007). In addition, prenylated isoflavonoids, especially the isoflavone-type skeleton could be considered as new lead compounds against breast cancer *via* protein tyrosine phosphatase 1B inhibition (Nguyen *et al*., 2012).

3.4.5. Other flavonoids

Amentoflavone (Fig. 4e), a biflavonoid from *Selaginella tamariscina* induces apoptosis in SiHa and CaSki cervical cancer cells by suppressing human papillomavirus protein E7 expression (Lee *et al*., 2011). The EtOH extract of the flowers of *Camellia nitidissima* Chi, a new acylated flavonoid glycoside, has been isolated, that is shown to inhibit proliferation and to induce apoptosis of human lymphoma U937 cells (Peng, Yu, Feng, Wang, & Shi, 2012). Also neohesperidin is a flavonoid compound found in high amounts in *Poncirus trifoliata*. It could induce apoptosis in human breast adenocarcinoma MDA-MB-231 cells that was associated with the activation of the Bcl-2/Bax-mediated signalling pathway (Xu *et al*., 2012).

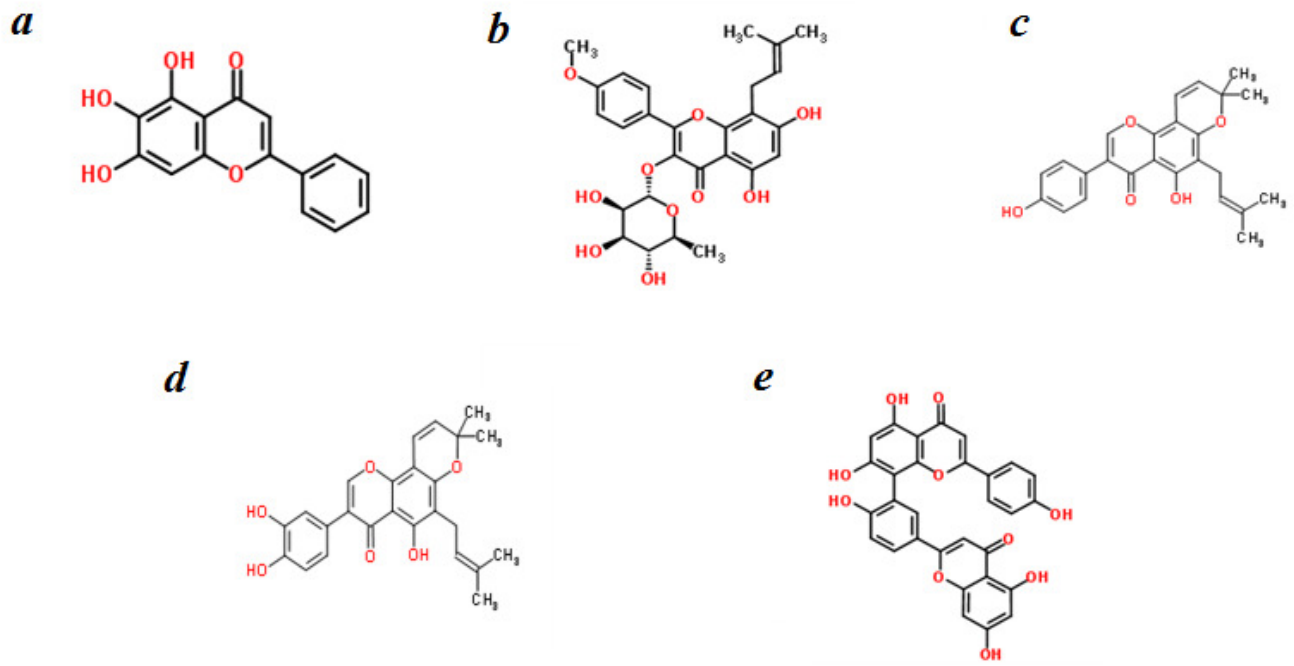

Fig. 4. Chemical structure of flavonoid. a, baicalein; b, baohuoside-I; c, osajin; d, pomiferin; e, Amentoflavone

3.5. Polysaccharide

3.5.1. Pulsatilla chinensis polysaccharides

One water-soluble polysaccharide was isolated and purified from the roots of *Pulsatilla chinensis*, it could improve both cellular and humoral immune response and might be explored as a potential natural antitumor drug (Liu *et al*., 2013). Besides, *Pulsatilla chinensis* polysaccharides (PCPS) had strong antitumor activity, and showed a significant anti-proliferative effect on C6 glioma *in vitro* assay. Meanwhile a remarkable inhibitory effect PCPS on the growth of C6 glioma and prolongation of life survival could be observed *in vivo*, it could be considered as a possible candidate drug for the glioma therapy (Zhou *et al*., 2012).

3.5.2. Lycium barbarum polysaccharides

Lycium barbarum polysaccharide (LBP) is extracted from the *Lycium barbarum*, and has potential anticancer activity. *In vitro* study showed that LBP could on dose-and time-dependently inhibit the growth of both PC-3 and DU-145 cells. *In vivo* experimental results indicate that LBP might significantly inhibit PC-3 tumor growth in nude mice (Luo *et al*., 2009). Miao *et al*. (2010) suggest that induction of cell-cycle arrest participates in the anticancer activity of LBP on gastric cancer cells. In addition, the *Lycii cortex radicis* extract may serve as a potential therapeutic agent for malignant human glioblastomas (Jeong, Kim, Kim, Kwon, & Kim, 2012).

3.5.3. Ganoderma lucidum polysaccharides

The potential utilization of a novel polysaccharide preparation as an adjuvant to conventional treatments of

tumor and its use for tumor prevention was isolated from the fruiting body of Ganoderma (Pang *et al*., 2007). Furthermore, polysaccharides were isolated from *Ganoderma lucidum*, it showed Potential antitumor activity and against solid tumor of Ehrlich's ascites carcinoma cells (Joseph, Sabulal, George, Antony, & Janardhanan, 2011). In addition, the novel polysaccharide SeGLP-2B-1 isolated from Se-enriched *Ganoderma lucidum*, showed anti-proliferative activity towards several cancer cell lines *in vitro*. It induces apoptosis *via* a mitochondria-mediated pathway (Shang *et al*., 2011).

3.5.4. Angelica polysaccharides

A novel polysaccharide isolated from *Angelica sinensis*, named APS-1d showed cytotoxic activity towards several cancer cell lines *in vitro*. The study indicated that APS-1d is capable of inhibiting HeLa cell proliferation and inducing apoptosis in these cells which primarily involves the activation of the intrinsic mitochondrial pathway (Cao *et al*., 2010). Three acidic polysaccharides (APS-3a, APS-3b and APS-3c) were obtained from *Angelica sinensis* (Oliv.) Diels. They displayed different structural features and anti-tumor activities. APS-3b and APS-3c significantly inhibited the growth of S180 tumors and increased the life spans of S180 tumor-bearing mice (Cao *et al*., 2010).

3.5.5. Solanum nigrum linne polysaccharides

A study showed the effect of the crude polysaccharides isolated from *Solanum nigrum* Linne (SNL-P) on tumor growth. SNL-P had a significant growth inhibition effect on cervical cancer (U14) of tumor-bearing mice (Li, Li, Gao, Han, & Lu, 2009). Further analysis indicated that the number of apoptotic tumor cells increased significantly This might correlate with the reduction of TNF-alpha level of blood serum, which resulted in a massive necrosis in tumor tissues and the up-regulation of Bax and down-regulation of Bcl-2 and mutant p53 gene expression, which triggered apoptosis in tumor cells (Li *et al*., 2007).

3.5.6. Others

The study suggested that polysaccharide PST001 isolated from the seed kernel of *Tamarindus indica* has immunomodulatory and tumor inhibitory activities and has the potential to be developed as an anticancer agent and immunomodulator either as a sole agent or as an adjuvant to other chemotherapeutic drugs (Aravind, Joseph, Varghese, Balaram, & Sreelekha, 2012). The polysaccharide from tea seed obtained by water extraction also had a potential application as natural antitumor drugs (Wei, Mao, Cai, & Wang, 2011). And, many ingredients from apples have been proven to have antitumor potency, low molecular weight apple polysaccharides could inhibit the development of colorectal cancer through affecting cell cycle, and it has potential for clinical prevention for colon cancer (Lu *et al*., 2010; Li *et al*., 2012).

3.6. Polyphenol

3.6.1. Resveratrol

Resveratrol (Fig. 5a), a polyphenol, which has been found in various plants, including grapes, passion fruit, white tea, and Japanese knotweed, displays a wide spectrum of biological activity. It exhibits potential antitumor properties as suggested by reducing cell proliferation and metastasis and inducing apoptosis, including leukemia, lymphoma; cancers of the breast, prostate, colon and melanoma. The growth-inhibitory and proapoptotic effects of piceatannol are mediated through cell-cycle arrest (Piotrowska, Kucinska, & Murias, 2012). Resveratrol's anti-tumor actions in prostate cancer could be explained, through inhibition of Akt/miR-21 signaling pathway (Sheth *et al*., 2012). And, resveratrol efficiently triggers apoptosis by a concentration- and time-dependent manner in bladder cancer cells through the intrinsic mitochondrial-dependent pathway (Stocco *et al*., 2012). Resveratrol might have great pharmacological promise in the treatment of bladder cancer (Lin, Wu, Huo, Zhang, & Jin, 2012).

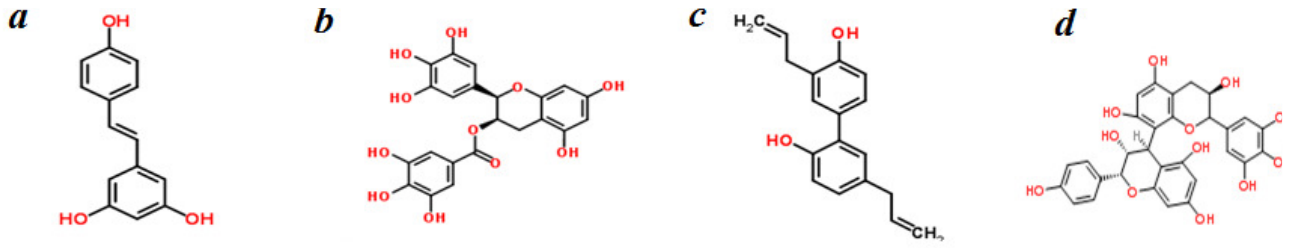

Fig. 5. Chemical structure of polyphenol. a, resveratrol; b, epigallocatechin gallate; c, honokiol; d, proanthocyanidin

3.6.2. Green tea polyphenol

A study had evaluated apoptosis and significantly decreased invasion activity of green tea polyphenols (GTP) and its principal constituent Epigallocatechin gallate (EGCG) (Fig. 5b) in MDA-MB-231 human breast cancer cell line (Thangapazham, Passi, & Maheshwari, 2007). GTP is a

candidate therapeutic for osteosarcoma that mediates its antiproliferative and apoptotic effects *via* activation of caspases and inhibition of NF-kappaB (Hafeez *et al*., 2006). EGCG selective anti-angiogenic effects on tumor-associated endothelial cells and endothelial progenitor cells. It could be a promising angiogenesis inhibitor for tumor therapy (Ohga *et al*., 2009). In addition, the study reports the antiproliferative and apoptosis-mediated cytotoxic effects of green tea and ginger polyphenolic extracts on human H460 cell line, indicating their promising chemopreventive effect against lung cancer (Hessien, El-Gendy, Donia, & Sikkena, 2012).

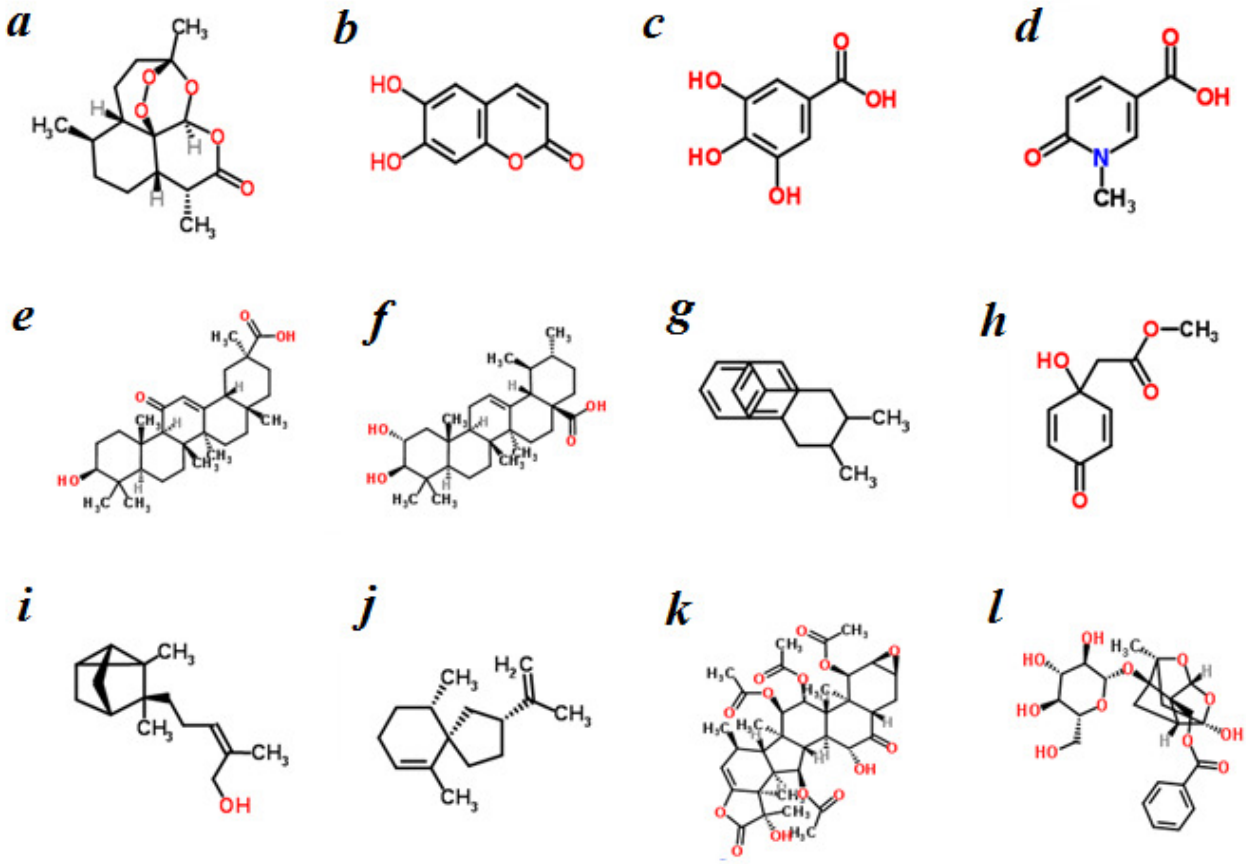

Fig. 6. Chemical structure of various natural product. a, Galactosylated artemisinin; b, Aesculetin; c, Gallic acid; d, Gambogenic acid; e, Glycyrrhetinic acid; f, Corosolic acid; g, Lignan; h, Jacaranone; i, α-Santalol; j, Mastic oil; k, Taccalonolides; l, Paeoniflorin

3.6.3. Honokiol

Honokiol (HNK) (Fig. 5c) is a small organic molecule purified from magnolia species and has demonstrated antitumor activities in a variety of tumor cell lines. Honokiol inhibited the growth and proliferation of oral squamous cell carcinoma cells *in vitro* (Chen *et al*., 2011). Honokiol treatment could potentially be a rational therapeutic strategy for breast carcinoma (Nagalingam, Arbiser, Bonner, Saxena, & Sharma, 2012). Honokiol also markedly inhibited peroxisome proliferator-activated receptor-gamma and COX-2 expressions in gastric tumor cells and tumors of xenograft mice, and induced apoptosis and cell death (Liu *et al*., 2010). The potential of honokiol to increase the antitumor effect of cisplatin when the agent and drug were combined that Liposomal honokiol may augment the induction of apoptosis in CT26 colon cancer models cells *in vitro* and *in vivo*, and this combined treatment has exhibited synergistic suppression in tumor progression according to the synergistic analysis (Cheng *et al*., 2011).

3.6.4. Proanthocyanidin

Grape seed proanthocyanidin (Fig. 6d) extract (GSPE) exhibited cytotoxicity towards some tumor cells, while enhancing the growth and viability of the normal cells which were examined. GSPE were observed on the MCF-7 breast cancer, lung cancer and gastric adenocarcinoma cells (Ye *et al*., 1999). A recent study found that Grape seed proanthocyanidins inhibited colon tumor-induced

angiogenesis and the growth of colon tumor xenografts on the chick chorioallantoic membranes (Huang *et al*., 2012). And it may be a promising candidate for head and neck squamous cell carcinoma therapy (Prasad & Katiyar, 2012). GSPs could significantly inhibit the growth of Sarcoma 180 tumor cells *in vivo* and remarkably increase thymus and spleen weight of Sarcoma 180-bearing mice and upgrade the secretion level of tumor necrosis factor-αin serum (Tong, Song, Sun, Sun, & Du, 2011). Besides, the antitumor effects of an anthocyanin-rich extract from black rice against human breast cancer cells, *in vitro* and *in vivo* induced apoptosis and suppressed angiogenesis (Hui *et al*., 2010).

3.6.5. Other polyphenolic compounds

The human breast cancer cell line, estrogen receptor negative, MDA-MB231, was used to evaluate the antitumor effect of polyphenolic extracts from the edible part of artichokes. Treatment of tumor cells reduced cell viability and inhibited cell growth in a dose-dependent manner. Importantly, it didn't have any effect on normal breast epithelial cell line MCF10A (Mileo *et al*., 2012). 2-(3,4-dihydroxyphenil)-ethanol (DPE), a polyphenol present in olive oil, that *in vivo* DPE antitumor effect is associated with anti-inflammatory and antiangiogenic activities resulting from the downregulation of the HIF-1alpha/mPGEs-1/VEGF axis (Terzuoli *et al*., 2010).

3.7. Others

Galactosylated artemisinin (Fig. 6a) induced apoptosis of Hela cell. It exhibits great antitumor activities, which may be related to triggering cytochrome apoptotic pathway mediated by BCL-2 family (Ren *et al*., 2012). The source of limonoids that are considered a natural antitumor herbal medicine (Zhao *et al*., 2010). Aesculetin (Fig. 6b) is an important coumarin found in various plant materials. It has been shown to have antiproliferative effects on several types of human tumor cells. Aesculetin induces apoptosis in HeLa cells through a ROS-mediated mitochondrial dysfunction pathway (Yang, Xiao, He, Qiu, & Hu, *et al*., 2010).

Gallic acid (GA) (Fig. 6c) is widely distributed in various plants and foods. It induced HeLa cell death accompanied by ROS increase and GSH depletion (You, Moon, Han, & Park, 2010). The gambogenic acid (GNA) (Fig. 6d) significantly inhibited the proliferation and apoptosis-induction and cell cycle arrest of several tumor cell lines *in vitro* and *in vivo*. Treatment with GNA induced A549 cells apoptosis (Li *et al*., 2010). Glycyrrhetinic acid (GA) (Fig. 6e) exhibited the tumor cell-selective toxicity through H-Ras downregulation, and its selectivity was superior to those of all the clinically available antitumor agents examined. Yu *et al*. (2010) suggested that GA with its cytotoxic effects could be utilized as a promising chemopreventive and therapeutic antitumor agent. Corosolic acid (Fig. 6f) significantly inhibited cell viability by both a dose- and time-dependent manner, and treatment induced S cell-cycle arrest and induced apoptosis associated with the activation of caspases *via* a mitochondrial pathway in HeLa cells (Xu *et al*., 2009). Recently, numerous lignan (Fig. 6g) derivatives isolated from plants have been proven to have the potential as an antitumor substance. The methanolic extract from the trunk of *Tilia amurensis* Rupr has antitumor compounds (Kim *et al*., 2011). 10 lignan derivatives (1-10) including two new lignan glycosides named tiliamurosides A and B were isolated and identified. Tiliamuroside B and schizandriside showed significant cytotoxicity against lung carcinoma, ovary malignant ascites, skin melanoma, and colon adenocarcinoma cell lines with inhibitory concentration values (Kim, Moon, Kim, Choi, & Lee, 2012).

A petroleum ether-soluble extract of the roots of *Onosma paniculata*, has been shown to affect the cell cycle and to induce apoptosis in melanoma cells, the isolation of several shikonin derivatives, Naphthoquinones, exhibited strong cytotoxicity against eight tumor cell lines and MRC-5 lung fibroblasts, found to possess the most potent cytotoxicity toward four melanoma cell lines (Kretschmer *et al*., 2012). Recently, Massaoka MH *et al*. isolated Jacaranone (Fig. 6h) from Pentacalia desiderabilis, a benzoquinone derivative that showed a broad antitumor activity and protective anti-melanoma effect in a syngeneic model. It's antitumor activity was shown against several human cancer cell lines *in vitro*. The results provide evidence for the mechanisms of action of Jacaranone and emphasize the potential use of this quinone for the treatment of melanoma (Massaoka *et al*., 2012). The α-santalol (Fig. 6i), a major component of sandalwood oil, has been reported against the development of certain cancers such as skin cancer both *in vitro* and *in vivo*. The apoptotic effects of α-santalol in inhibiting the growth of human prostate cancer cells have been revealed (Bommareddy, Rule, VanWert, Santha, & Dwivedi, 2012). Mastic oil (Fig. 6j) from *Pistacia lentiscus* variation chia. Presently, Magkouta *et al*. (2009) demonstrated that treatment of immunocompetent mice with mastic oil significantly inhibited tumor growth without toxicity. Analysis indicated that this effect is associated with increased apoptosis, reduced neovascularization, and inhibition of chemokine expression. It reduced vascular endothelial growth factor and chemokine release by Lewis lung carcinoma cells (Li *et al*., 2011). The Taccalonolides (Fig. 6k) are a class of microtubule stabilizing agents that do not bind directly to tubulin isolated from plants of the genus Tacca. Li *et al*. (2011) isolated five new Taccalonolides from one fraction of an ethanol extract of *Tacca plantaginea*. The potencies of Taccalonolides and their direct interaction with tubulin, together with the previous excellent *in vivo* antitumor activity of this class, reveal the potential of the Taccalonolides as new

anticancer agents (Peng *et al*., 2011). Zhang *et al*. (2011) determined, Paeoniflorin (Fig. 6l), the principal bioactive component in the Paeony root, can induce significantly the apoptosis of HeLa cells, which may be demonstrated by the down-regulation of anti-apoptosis gene Bcl-2 and the up-regulation of pro-apoptosis genes Bax and caspase-3.

4. Potential

Natural product discovery suffers from lack of broader pharmaceutical industry support, several technological developments over the past several years are reducing the complexity of working and building these extracts. Therapeutic properties and medicinal benefits of natural products can be linked to the presence of a wide array of bioactives especially alkaloid, diterpenoid, triterpenoid, polysaccharide, polyphenols and flavonoids. Natural products have been the source of most of the active ingredients of medicines (Wang *et al*., 2013; Zhang *et al*., 2012). This is widely accepted to be true when applied to drug discovery in 'olden times' before the advent of high-thoroughput screening and the post-genomic era: more than 80% of drug substances were natural products or inspired by a natural compound (Harvey, 2008). We believe that natural product research has enormous yet unexploited potential, and describe the important advantages of natural product derived molecules as drug candidates for development.

5. Conclusion

There are many promising drug candidates in the current development pipeline that are of natural origin. Technology associated with natural product research have been improved, so there are better opportunities to explore the biological activity of previously inaccessible sources of natural products. The phytochemical research based on ethnopharmacology is considered an effective approach in the discovery of novel chemicals entities with potential as drug leads. Furthermore, we focus on the discovery and biological evaluation of the natural products, which is due to the increasing incidence of malignant cancers and drug multi-resistance. The natural product compounds have been considered the driving force for drug discovery. With the increasing acceptance that the chemical diversity of natural products is well suited to provide the core scaffolds for future drugs, there will be further developments in the use of novel natural products based on natural products in drug discovery activity, as a mechanism of tumor prevention by some of the most studied naturally occurring plant compounds.

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