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Perspective Studies on Novel Anticancer Drugs from Natural Origin: A Comprehensive Review

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Abstract: Cancer occurs when alterations of genetic material create an abnormal function leading to unregulated proliferation of cells in the body. Cancer remains as one of the most predominant illnesses causing death, where each year more than 10 million people are identified worldwide. Due to restrictions and side effects observed from various chemotherapeutic anti-cancer drugs, as well as thousands of secondary metabolites formed in plants and other natural organisms, there is a high trend, toward novel drug discovery from natural sources. It seems that high throughput screenings based on reverse pharmacology and reverse pharmacognosy might result in more successful approaches in the future. The main objective of this review is to exhibit an up-to-date comprehensive overview on the recently identified natural antitumor compounds from various natural origins including plants, fungi, endophytic fungi and marine organisms. In order to facilitate the anticancer drug discovery and development, new strategies might be considered such as biotechnology and nanoparticle targeting approaches. The reverse pharmacognosy and its complementary the reverse pharmacology which are associated with high throughput screening, virtual screening and knowledge databases from traditional medicine, provide successful and strong tools to accelerate the process of future drug discovery.

Key words: Aquatic organisms, drug discovery, biological products, fungi, neoplasms, plants, review

INTRODUCTION

Undoubtedly, cancer is an important chronic illness, in which accumulation of DNA alterations and damages may be one of the most considerable causative parameters. It is revealed that environmental stresses such as infection, food additives, chemicals and air particles could create damages in the cells, of which DNA alteration is a serious consequence leading to carcinogenesis. A living organism has multiple mechanisms to manage the environmental stress. For instance, immune responses, apoptosis, cell cycle control and induction of antioxidative enzymes are such examples (Hiramatsu *et al*., 2006). It seems that various common types of cancer such as breast, colon and prostate cancers are initiated through genetic and environmental interactions. Previous literature revealed that a small number of patients get cancer due to alterations in the germ cells whereas most cancers are the result of genetic alterations at the somatic cells (Hiramatsu *et al*., 2006; Stankovic *et al*., 2006). Giving benzene as an example, although most of studies are focused on neoplastic effects ahead of non-neoplastic effects, the exact mechanisms have not been fully understood (Bahadar *et al*., 2014). However, particular genes have been recognized in different types of cancer, in which accumulation of the mutations may lead to the tumor initiation in cells, although this remained elusive so far. The identification of the cellular origins of cancer is also critical to increase our knowledge about the mechanisms regulating the various stages of tumors. In the other words, introducing just an effective compound against neoplastic cells is not enough but the cellular mechanisms of actions should be identified (Momtaz *et al*., 2013). Most recently, lineage-tracing experiments have been employed to mark individual tumor cells and assess their respective contribution to tumor growth and relapse after therapy (Blanpain, 2013).

Reactive Oxygen Species (ROS) are found to hurt the biological organisms and molecules, such as lipids,

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protein and DNA resulting in initiation of the cancer. Regarding this point, for many years, it was thought that antioxidants can be effective in prevention and treatment of cancer by free radical scavenging and prevention of DNA alterations. In fact, oxidation generally happens in all oxygen-rich environments during exposure of a compound to ultraviolet light or heat. Polyunsaturated fats can be oxidized in the presence of oxygen resulting in a chain reaction and amplification of the basic oxidative damage (Buzzai *et al*., 2005; Liu *et al*., 2011; Momtaz *et al*., 2013). Moreover, ROS can play a role as a trigger to initiate carcinogenesis by permanent damaging of DNA and causing mutations in p53 and the tumor suppressor gene as well. Furthermore, ROS are able to modulate the activity of several transcription factors like nuclear factor kappa B (NF-κB) and activator protein 1 (AP-1) that play a regulatory role for the Jun and c-Fos as two nuclear oncoproteins. The mentioned mechanisms play roles in initiation, promotion and progression of cancer. However, interestingly, adequate levels of ROS may show opposite effects in inhibition of carcinogenesis through enhancing p53 expression and inducing tumor cell apoptosis (Khosravi-Far and White, 2008; Alawadi *et al*., 2011).

Moreover, antioxidants such as vitamin C and E can interfere with some of chemotherapeutic drugs which need free radicals and oxidative stress condition to act (Saeidnia and Abdollahi, 2012, 2013a). For these reasons, many oncologists Now-a-days recommend to their patients not to take vitamin supplements during chemo or radiotherapies (Bagchi and Preuss, 2005; Watson, 2013).

Actually, there is a serious concern on taking or avoiding the antioxidative supplements during chemotherapy and chemoprevention which has been already criticized in details (Abdollahi and Shetab-Boushehri, 2012; Saeidnia and Abdollahi, 2012, 2013a). The understanding of the mechanism of action of anticancer drugs is very important. Some anticancer agents like paclitaxel could attack the cancer cells through generation of ROS or interfering with ROS metabolism. Also, there are a few anti-angiogenesis compounds like endostatin that can be an anti-neoplastic medicine when employed together with another chemotherapeutic agent. Additionally, some natural anticancer agents like piperlongumine bind to the active sites of several key cellular antioxidants including glutathione S transferase and carbonyl reductase 1 only in cancer cells (Schafer *et al*., 2009; Saeidnia and Abdollahi, 2013a). Regarding the similarity between mechanisms of aging and cancer (Hasani-Ranjbar *et al*., 2012; Momtaz and Abdollahi, 2012), the thought about usefulness of antioxidants in prevention of aging or cancer is logically true but when aging or cancer started then use of antioxidants cannot be that helpful especially if chemotherapies are started in cancer (Saeidnia and Abdollahi, 2013a). However, in this study, we aimed to review the novel natural anticancer drugs from plants, fungi, endophytic fungi and marine origins, especially those recently introduced and discuss about their mechanism of action suggested by investigators in the recent publications.

HISTORY OF USING NATURAL ANTICANCER DRUGS

There are some documents originated from the ancient civilizations of Asia and Middle East countries, in which the application of herbal medicines to keep the health of human being is explained (Wang *et al*., 2010). Among the Egyptian herbal medicines, some plants including opium, cannabis, myrrh, fennel, cassia, thyme, henna, juniper, aloe, linseed, castor, caraway seeds, marjoram, spearmint, peppermint and so on have been described. There is mirrored evidence available in traditional Chinese medicine and Ayurveda to prove the usage of such herbal remedies (Patwardhan and Mashelkar, 2009). Traditional Iranian medicine also contains good information on medicinal plants, of which, yarrow, savory and sage are good examples (Saeidnia *et al*., 2005, 2009, 2011; Gohari *et al*., 2010, 2012).

An appraisal of the currently used anticancer agents showed that many anticancer drugs are mainly from natural origin as well as their semi-synthetic products. However, even synthetic drugs are designed according to natural products as the leads. As far as we could ascertain, 69% of the approved anticancer agents since 1980-2002 are originated or developed from natural sources (Newman and Cragg, 2007; Liu *et al*., 2009). About 43-80% of patients with prostate cancer are under treatment by complementary and alternative medicines. A group of those patients had important history of prostate cancer in their families, while another group was on active surveillance and the latter ones experienced failure or were on androgen deprivation and tried to postpone the progression of cancer by use of natural remedies (Trottier *et al*., 2010). Although, plants are considered as the main sources of anticancer drugs, only 5-15% of the approximately 250,000 species of higher plants have been studied for the presence of bioactive compounds and this is why there is a huge potential to exploit nature for new anticancer compounds. Opposite to Western medicine which applies purified compounds and targets a single physiological endpoint, various traditional medicines employ mixed or combination of herbal remedies (Monneret, 2010).

Now-a-days, many epidemiologists emphasize that decrease of cancer risk is related to consumption of particular species of vegetables and fruits suggesting that phytoceuticals (herbal based food products) may possess cancer preventive properties. Among the approved anticancer agents, there are many natural compounds including doxorubicin, daunomycin, mithramycin, paclitaxel, vinblastine and vincristine. Furthermore, numerous synthetic compounds like flavopiridol, combretastatin and roscovitine have been listed as the anticancer agents (Cho, 2011).

CONVENTIONAL AND ADVANCED CANCER TREATMENTS

Today, there are some general management for diverse kinds of cancers such as surgery, radiation and chemotherapy. Surgery is often used for removal of a tumor as the first treatment. However, it has disadvantages including potential damages to normal cells and tissues. Radiation therapy with X or gamma rays is widely used to induce death or apoptosis in cancerous cells in order to preserve the tissues surrounding a tumor and to destroy all cancerous cells as well. Anyhow, this method cannot remove metastatic cells and meanwhile causes several adverse effects like weakening of the immune system. The latter method "chemotherapy" is defined as the systemic administration of anticancer agents which could migrate through the blood toward the cancerous tissues. The main purpose of chemotherapy is to wipe out all cancerous cells in the body even metastatic cells. But there are many kinds of common cancers that are not treated with chemotherapy alone and on the other side, different adverse effects might occur including nausea, anemia, weakening of the immune system, diarrhea, vomiting and hair loss. Resistance to chemotherapeutic drugs is also another disadvantage of this treatment (Cho, 2011). Usually, chemotherapy is recommended through systemic circulation for larger tumors or in case of metastasis into lymph nodes. Chemotherapeutic agents are mainly molecules with high volume of distribution which facilitates to reach up an adequate therapeutic level in tumor cells. For this reason, normal tissues are irreversibly exposed to the chemotherapeutic compounds resulting in adverse effects such as nausea, vomiting, alopecia (hair loss), anorexia (poor appetite) and bone marrow suppression. On the other hand, critical bioavailability is observed with high molecular weight chemotherapeutic drugs in comparison to low molecular weight ones which tends to have quick excretion rate from the body. Besides, drug resistance remains as one of the most important disadvantages of chemotherapy. In order to conquer drug resistance or multidrug resistance, the above drawbacks should be minimized by developing more effective site specific drug delivery systems which can significantly improve the therapeutic efficacy to chemotherapeutic drugs with minimal toxicity (Hu and Zhang, 2009; Egusquiaguirre *et al*., 2012).

There are advanced methods of cancer treatment via immunotherapy. It is found that, cancer cells should be targets of the host immune responses in a normal condition. Cells and molecules of the immune system are important in determining the anti-tumor immune response. Now-a-days, different strategies are being progressed to increase the anti-tumor immune responses, such as DC-based vaccines and antagonists of inhibitory signaling pathways to overcome immune check-points (Alderton and Bordon, 2012). Recently, monoclonal antibodies have indicated a broad spectrum of antigens which are presented in human cancer cells and correlated to abnormal proteins from DNA mutations. Over the past couple of decades, the US Food and Drug Administration (FDA) approved a number of monoclonal antibodies to treat certain cancers while the scientists discovered more antigens linked to various types of cancer. Two types of monoclonal antibodies are employed in treatments including naked (no drug or radioactive material attached to them) and conjugated (joined to a chemotherapy drug, toxin, or a radioactive particle) antibodies (ACS, 2014).

Although, the cancer vaccination is an old idea, today cancer immunotherapy can be categorized to four aspects: Active, passive, none-specific and adoptive therapies (Hamdy *et al*., 2011a, b). Advanced cancer therapies reveal the application of tissue-specific cytotoxic agents. For instance, interleukin 13 (IL-13)-conjugated liposomes carrying cytotoxic agents are introduced as an approach for creating a nanovesicle drug delivery system in brain tumor therapy. With no doubt, treatment of malignant brain tumors has many difficulties. Therefore, developing a delivery system for chemotherapeutic agents is really crucial in order to ablate individual cancer cells without diffusing to surrounding brain tissues (Madhankumar *et al*., 2006; Cho, 2011).

ANTI-CANCER AGENTS FOR THERAPY AND PREVENTION

Well-known approved natural anticancer agents: Some of the important examples of anticancer drugs that are approved in clinical use originated from plants are overviewed and summarized in Table 1. However, there is a major problem with cancer chemotherapy called

Table 1: Main examples of approved natural anticancer medicines (Cho, 2011)

Drugs	Lead natural compound/plant	Mode of action	Clinical Application
Daunomycin	*Streptomyces peucetius*	Topoisomerase II inhibitor, intercalating agent	Acute myeloid/lymphoblastic leukemia
Doxorubicin	*Streptomyces peucetius*	Topoisomerase II inhibitor, intercalating agent	Acute lymphoblastic leukemia, breast, ovarian, small cell, lung, thyroid, bladder, bone sarcoma and gastric cancers, Hodgkin's lymphoma, neuroblastoma
Etoposide	American mayapple	Topoisomerase II inhibitor	Testicular cancer
Paclitaxel	Pacific yew tree	Tubulin polymerization acceleration	Breast, ovarian, non-small cell and lung cancers, hormone refractory prostate cancer, Kaposi's sarcoma
Teniposide	Podophyllotoxin	Breaking single and double strand DNA	Acute lymphoblastic leukemia
Vinblastine Vincristine	Madagascar periwinkle	Inhibiting the tubulin polymerization	Bladder cancer, lymphoma, Kaposi's sarcoma, myeloma

resistance to chemo-therapeutic medicines, since the defective apoptotic pathway may result in clonal progression of resistant transformed cells (Kashkar, 2010). Among the mentioned drugs in Table 1, docetaxel is widely applied as a usual care in patients with prostate cancer in order to cause death of cancer cells among androgen independent cells. Literature reveals that in hormone-refractory metastatic prostate cancer, docetaxel plus prednisone could improve prostate specific antigen response rate, pain and health-related quality of life. Moreover, It is also mentioned that docetaxel plus estramustine were able to enhance progression-free survival (McKeage and Keam, 2005). Although, docetaxel-based chemotherapy is well-known as the standard first-line therapy in metastatic Castration-Resistant Prostate Cancer (CRPC), most patients finally develop resistance to this treatment. In a recent study, the alteration in expression of 18 selected genes were investigated by real-time quantitative reverse transcriptase PCR in cell lines and in about 11 FFPE (formalin-fixed, paraffin-embedded) and five optimal cutting temperature tumor samples. The results indicated a down-expression of CDH1 and IFIH1 in docetaxel-resistant tumors (Marin-Aguilera *et al*., 2012). The reason should be related to transcription factor NF-κB which may contribute to chemo-resistance in prostate cancer cells as well as probable enhancing the high risk of relapse in patients with localized prostate cancer (Berthold *et al*., 2008; Karin, 2009).

Herbal medicines as the important sources of anticancer compounds: There are currently limitations in cancer chemotherapy approach, especially when all focus only on the mono-targeted approach. Actually, cancer happens as a result of many changes in a variety of genes and signaling processes. On the other hand, targeting different signaling elements might be the better approach. Regarding this point, medicinal plants, in both single and multiple applications, can conserve an amplified potential. Now-a-days, natural products particularly as combinational mixtures have revealed promise in pre-clinical models, of which pomegranate, green tea, soy and tomato paste are some examples (Kumar *et al*., 2010a). In this regard, the efficacy of tomato paste and broccoli (either alone or in combination) has been reported in comparison to lycopene in rodent models of prostate cancer (Kumar *et al*., 2010b). Here in this section, the efficacy of some plant-derived promising candidates for chemoprevention and chemotherapy is concisely discussed in the Table 2. It is noteworthy that most of data about natural products and their positive effects in various diseases although come from Asian countries traditional medicine, in most of cases only experimental studies have been completed and clinical parts have been remained vacant (Hosseini and Abdollahi, 2012; Sarwar *et al*., 2011).

Anticancer fungi: Besides medicinal herbs, there are many fungi found effective on various cancer cell lines that some of them could surpass the pre-clinical evaluations to become a promising candidate for further clinical tests. Among them, *Ganoderma lucidum* is a saprophytic fungus often growing well in a humid and ventilated condition with high temperature. In the modern systematics, it is classified as (Basidiomycotina) Ganodermoideae. This is one of the traditional medical fungi since ancient times. Phytochemical investigations revealed that its major constituents are polysaccharides, enzymatic proteins and glycoproteins and other bioactive compounds such as triterpenoids, steroids and fatty acids (Akihisa *et al*., 2007; Fukuzawa *et al*., 2008). Numerous biological functions have been reported for *G. lucidum*, including anticancer activity (Nonaka *et al*., 2006), life-protective effect (Yuen and Gohel, 2008) and antioxidation (Zhuang *et al*., 2009) as well. The anticancer activity of this fungus is mediated via different mechanisms such as cell cycle arrest at G2/M phase in human immune system-related cancer cells (Sadava *et al*., 2009), cell death via apoptosis (Calvino *et al*., 2010), inhibiting the invasion of HCT116 cells mediated by

Table 2: Several important herbal medicines that have been successful in pre-clinical studies of different types of cancer

Main constituents	Observations	References
Allium sativum		
Allicin, oil-soluble sulfur compounds, including diallyl sulfide, diallyl disulfide, diallyl trisulfide, allyl methyl trisulfide, dithiins and ajoenes, wsater-soluble garlic sulfur compounds (S-allylcystein or S-allylmercaptocysteine)	Preventive activity in cancer animal models, inhibiting cancer cell division, survival and metastasis both *in vitro* cell cultures and *in vivo* xenograft models (Fig. 1)	(Lawson and Wang, 2005; Chu *et al*., 2007; Herman-Antosiewicz *et al*., 2010)
Angelica sinensis		
Ferulic acid, ligustilide, brefeldin A, butylidenephthalide and polysaccharides	Inhibiting platelet activation, relieving vascular endothelial cell damage, improving microcirculation in ulcerative colitis, synergistic antiproliferative activity in combination with BCNU or carmustine, suppressing the cell cycles of glioblastoma and hepatocellular carcinomas in the G0/G1 phase and promote apoptosis	(Lin *et al*., 2008; Yu *et al*., 2010)
Astragalus membranaceus		
Astragaloside IV as a saponin	Pharmacologic effects havenot been completely determined, currently it is reported as immunomodulator	(Tanaka *et al*., 2008; Li *et al*., 2009)
Camellia sinensis		
Polyphenolic compounds like (-)-epigallocatechin-3-gallate (Fig. 2)	Preventing mammary tumorigenesis in TAg mice, experimental studies support the efficacy of green tea for cancer prevention but thereare only few human intervention studies	(Halder *et al*., 2008; Li *et al*., 2010)
Curcuma longa		
Curcumin (bis-α,β-unsaturated β-diketone)	Modulation of growth factors and their signaling pathway, effects on tumor suppressor p53 and mitogen-activated protein kinases, chemopreventive and chemotherapeutic activity, inhibiting of angiogenesis and metastasis	(Anand *et al*., 2008; Bar-Sela *et al*., 2010)
Hedyotis diffusa		
Flavones, anthraquinones and polysaccharides	Suppressing the growth of various cancer cells and inducing apoptosis in both *in vitro* and *in vivo*, cytotoxicity against cancerous cells, inhibiting some oncogenes and up-regulating anti-oncogenes immune modulating some functions against cancer, enhancing the activities of natural killer cells and macrophages, promoting the proliferation of spleen cells and up-regulating interleukin-2 and tumor necrosis factor-alpha	(Shi *et al*., 2010; Yang *et al*., 2010)
Panax ginseng, Panax quinquefolius		
Ginsenosides including 20(s) protopanaxadiol-type, 20(s) protopanaxatriol-type and oleanane-type	Ginsenosides showed interesting anticancer activities including inductionof apoptosis, inhibition of cell cycle progression and anti-angiogenic activity, studies on cancer chemotherapy in humans are rare but there are more reports on cancer prevention	(Yim *et al*., 2005; Xu *et al*., 2007; Jia and Zhao, 2009)
Scutellaria barbata		
Flavonones (scutellarein, scutellarin, carthamidin, socarthamidin, wogonin, apigenin and luteolon, pheophoride-a) as well as clerodane diterpeonoids	Successful to pass the second phase I of clinical trial, cytotoxicity, anti-proliferation activity, induction of apoptosis and expression of Bcl-2 against liver cancer cells but with a low cytotoxic effect on normal liver L-O2 cell lines	(Suh *et al*., 2007; Yu *et al*., 2007; Dai *et al*., 2009, 2010)

inhibition of nuclear translocation of NF-κB and degradation of IκB-α inhibitor (Chen *et al*., 2010) and inhibiting the early event in angiogenesis (Stanley *et al*., 2005).

However, *Ganoderma* is applied in combination with other herbs or foods (such as *Dendranthema morifolium*, *Panax pseudoginseng* and *Glycyrrhiza uralensis*) to treat cancer patients as an alternative medicine regarding to their synergistic efficacy (Kim *et al*., 2008a). The safety of this fungus is essential to be examined in clinical trials before administration to cancer patients, although no side effect has been reported in healthy subjects after oral taking the extract (2 g day^{-1}) for 10 days compared to placebo (Wicks *et al*., 2007).

Mushrooms are also applied in both traditional and modern clinical practice. Of them, macrofungus *Coriolus versicolor* is widely used so far. Modulation of innate and adaptive immunity, hematopoietic activity and direct toxic effects are recently reported in details (Cheng and Leung, 2008; Kim *et al*., 2008b). The main phytochemical constituents of this mushroom are polysaccharides (in particular β-D glucans),

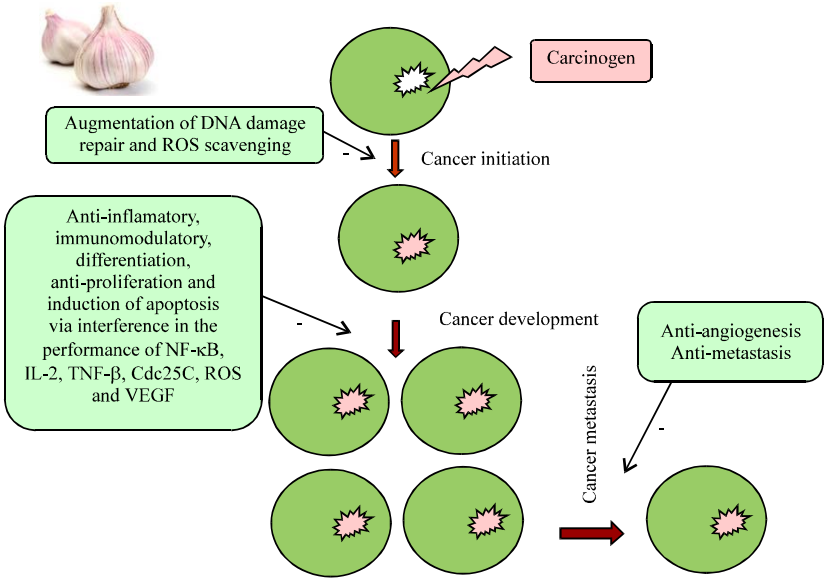

Fig. 1: Schematic interference of garlic metbolites in cancer initiation, promotion and progress. Garlic acts via interaction with cell division cycle 25C phosphate (Cdc25C), Interleukin 2, (IL-2), Nuclear Factor (NF-κB), Reactive Oxygen Species (ROS), Tumor Necrosis Factor (TNF-β) and Vascular Endothelial Growth Factor (VEGF)

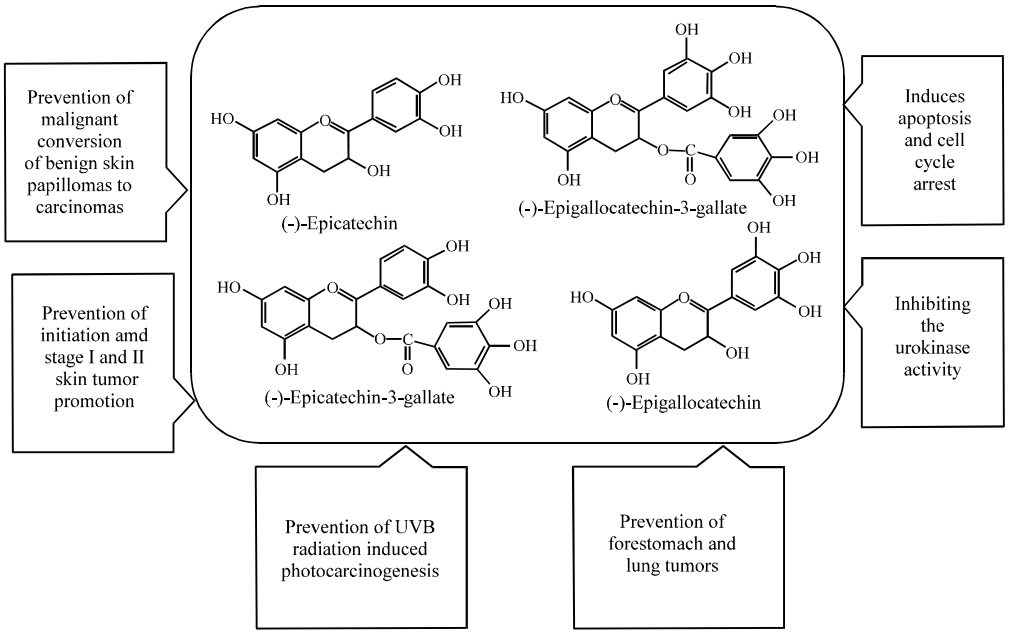

Fig. 2: Polyphenoles of green tea and their functions as the chemopreventive agents

polysaccharide peptide and protein-bound polysaccharides, as well as terpenoids, phenols, lipids and a number of small molecules (Rau *et al*., 2009). Not only the efficacy of polysaccharide portions of this mushroom in restoring the immune system in cancer patients is well reported but also potent anticancer activity of its compounds in inhibiting tumor cell proliferation or metastasis have been documented (Chan *et al*., 2009; Sadahiro *et al*., 2010). Numerous *in vitro* and *in vivo* studies as well as clinical trials have demonstrated that *Coriolus* is potentially a novel source of anticancer agents.

Another edible mushroom known as *Lentinus edodes* is widely used in Japan and China and also cultivated

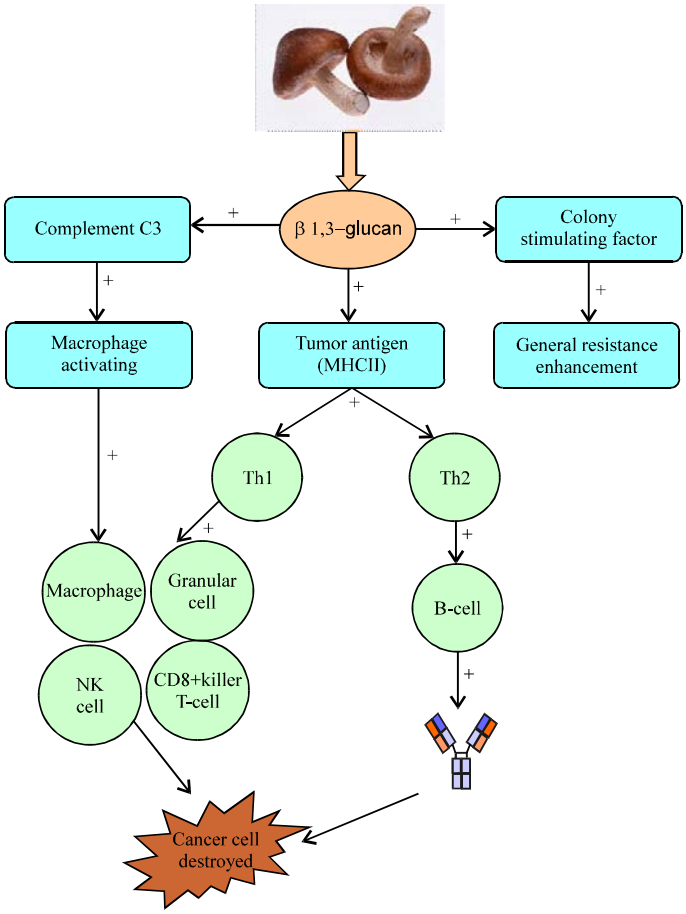

Fig. 3: Mechanism of anticancer activity of *Lentinus edodes*, Cluster of Differentiation 8 (CD8), Major Histocompatibility Complex (MHC), Natural Killer cells (NK) and T-helper (Th)

worldwide. Actually, the mentioned mushroom has been used from old times as a delicacy due to beneficial properties in human body. Phytochemical investigations revealed that several polysaccharides have been identified from this mushroom named: Lentinan, β-1, 3; 1, 6-D-glucans (Fig. 3), glycogen-like polysaccharides, α-1, 4; 1, 6-D-glucans, 1, 6-β-D-glucans with 1, 3 and 1, 4-β-bonded heteroglucans, heterogalactan, heteromannan and xyloglucan (Jong *et al*., 1983). Anticancer activity of its polysaccharides may be due to modulation of both innate and adaptive immunity by enhancement of the numbers and/or functions of macrophages and Natural Killer (NK) cells, as well as subsets of T cells (Akramiene *et al*., 2006). A schematic mechanism of anticancer activity of *Lentinus edodes* is shown in Fig. 3.

Clinical evaluations indicated that combinational therapy with lentinan/micellary β-1, 3-glucan and chemotherapy could prolong the lifespan of cancer patients (Yoshino *et al*., 2010). In one study at phase I clinical trial, the clinical safety and tolerability of AHCC (an extract of shiitake mushroom of the basidiomycete family of fungi rich in alpha glucans) has been reported. It is also mentioned in present study that 9 g of AHCC (150 mL day^{-1} of the currently available liquid AHCC) which was orally recommended for 14 days to 26 healthy subjects (both sexes and aged 18-61 years) caused various moderate side effects, including nausea, diarrhea, bloating, headache, fatigue and foot cramps. No abnormalities in the laboratory parameters have been reported and the administered dose was well tolerated in 85% of the persons (Spierings *et al*., 2007). This mushroom and its preparations are thought as a promising antitumor medicine, nonetheless the time of harvesting and keeping conditions may influence its biological properties and polysaccharide content.

Endophytic fungi: Endophytic fungi are endosymbiont fungi living within a plant for at least part of their life without causing apparent disease. Additionally,

endophytes are ubiquitous and have been found in many species of plants studied so far, although the relationships between endophytic fungi and plants have not been well understood (Faeth, 2009). They have special mechanisms to penetrate inside the host tissue and regarding their biotransformation abilities they synthesize many novel secondary metabolites. Actually, endophytic fungi produce such metabolites to compete with the epiphytes and/or the plant pathogens to maintain a critical balance between fungal virulence and plant defense (Chandra, 2012). Recently, anti-cancer activities have been reported for such endophytes. *Hypocrea lixii* is a new endophyte producing cajanol from the roots of pigeon pea that has been recently investigated for its potential toxicity towards human lung carcinoma cells (A549). However, the activity was evaluated *in vitro* but the importance of this study was in finding an alternative approach for large-scale production of a promising anti-cancer cajanol (Zhao *et al*., 2013). Furthermore, the anti-cancer activity of several endophytic fungi related to the Brazilian plant *Stryphnodendron adstringens* has been recently reported. The extracts of *Diaporthe* cf. *phaseolorum* and *Xylaria* sp., phylotypes exhibited *in vitro* cytotoxic activities (Carvalho *et al*., 2012). Moreover, camptothecine (CPT) is a well-known inhibitor of eukaryotic topoisomerase I.

There are several semi-synthetic derivatives of this quinoline alkaloid employing Now-a-days in clinic against ovarian, small lung and refractory ovarian cancers. This compound is generally produced by numerous plant species from Asterid clade. However, its other sources are endophytic fungi. The endophytes *Fomitopsis* sp., P. Karst, *Alternaria alternata* (Fr.) Keissl and *Phomposis* sp. (Sacc.), associated with the medicinal plant *Miquelia dentata* (Icacinaceae), have been studied for their abilities to produce CPT, 9-methoxy CPT (9-MeO-CPT) and 10-hydroxy CPT (10-OH-CPT). It was demonstrated that all the three fungi could produce above mentioned compounds in the artificial media. In addition, methanolic and ethyl acetate extracts of these endophytes displayed toxic activity against colon and breast cancer cells (Shweta *et al*., 2013). Another bioactive compound named sclerotiorin has been recently isolated from an endophyte *Cephalotheca faveolata* and found as an apoptosis inducer in colon cancer cells (HCT-116) via activation of BCL-2-like protein 4 (BAX) and down-regulation of B-cell lymphoma 2 (BCL-2) as well as cleaving caspase 3 (Giridharan *et al*., 2012). An endophytic fungus, coded as PM0651480 has been isolated from the leaves of the plant *Mimosops elengi* (Sapotaceae). Its extract displayed good anti-inflammatory and anticancer activity due to presence of ergoflavin which induced considerable toxicity in ACHN, H460, Panc1, HCT116 and Calu1 cancer cells (Deshmukh *et al*., 2009). In another study, about 81 Thai medicinal plant species were collected from different regions of Thailand and evaluated for presence of possible bioactive endophytic fungi. Literature revealed that about 60 fungi were active against human oral epidermoid carcinoma cells (EC_{50} 0.42-20 μg mL^{-1}) and also about 48 fungi showed toxicity against breast cancer cells (EC_{50} 0.18-20 μg mL^{-1}) (Wiyakrutta *et al*., 2004). *Penicillium melinii Yuan*-25 and *Penicillium janthinellum* Yuan-27 (extracted from the roots of *Panax ginseng*), are also reported to possess anti-cancer activity due to diverse bioactive compounds known as linesginsenocin, methyl 2, 4-dihydroxy-3, 5, 6-trimethylbenzoate, 3, 4, 5-trimethyl 1, 2-benzenediol, penicillic acid, mannitol, ergosterol and ergosterol peroxide which all exhibited anti-cancer activity (Zheng *et al*., 2013). A dditionally, the EtOAc extract of a culture broth of the endophytic fungus *Perenniporia tephropora* Z41 from a variety of *Taxus chinensis* is reported to display significant toxicity (IC_{50} values: 2-15 μg mL^{-1}), while its active components perenniporin A, rel-(+)-(2aR, 5R, 5aR, 8S, 8aS, 8bR)-decahydro-2, 2, 5, 8-tetramethyl-2H-naphtho[1, 8-bc] genfuran-5-ol (3) and albicanol indicated moderate toxicity (IC_{50} values: 6-58 μg mL^{-1}) (Wu *et al*., 2013). In conclusion, endophytic fungi are relatively novel sources of anti-cancer agents, thus investigations continue. Further animal and clinical studies are essential to prove whether they can find a place among future chemotherapeutic agents.

Anticancer compounds from marine sources: For many years, anticancer drug discovery has concentrated on discovery of new bioactive compounds from higher plants due to simplicity and accessibility. Recently, other organisms including marines (like marine algae) have been considered, since not only the access to those organisms became streamline because of progress in marine technology but also many scientific developments occurred in the areas of chromatography and spectroscopy in order to simplify isolation and structural elucidation of the natural products. Going through a vast bibliography shows that marine organisms have indicated a diverse biological and pharmacological activities including: Anticancer, antimicrobial, anti-inflammatory, antispasmodic, antiviral, antioxidant and enzyme inhibition activities (Kintzios and Barberaki, 2004). As far as we could ascertain, the anticancer activity of some marine organisms have been reviewed so far (Kintzios and Barberaki, 2004). In this regard, the impressive results of anticancer activity for some marine algae together with

Table 3: Recently reported anticancer activity from marine algae and other marine organisms

Marine organisms	Metabolites/Chemistry	Activity	References
Brown algae	Carotenoid fucoxanthin	Arresting the growth of LNCap prostate cancer cells via suppression in the G1 phase	(Satomi, 2012)
Callophyllis japonica	Ethanol extract	Inhibiting H_2O_2-induced cellular apoptosis and activating cellular antioxidant enzymes	(Kang *et al*., 2005)
Capsosiphon fulvescens	Polysaccharides	Inducing the apoptosis of gastric cancer cells via the PI3K/Akt pathway	(Kim *et al*., 2012)
Costaria costata	Fucoidans	Anticancer activity on human colon cancer cells	(Ermakova *et al*., 2011)
Eclonia cava	Fucoidans	Anticancer activity on human colon cancer cells	(Ermakova *et al*., 2011)
Gracilaria corticata	Aqueous extract	Inhibition of the proliferation of human leukemic cell lines	(Zandi *et al*., 2010b)
Gracilaria tenuistipitata	Ethanol extract	Increasing the recovery of cells from H_2O_2-induced DNA damage, counteracts cellular proliferation and induced G2/M arrest, Anti-proliferative activity on Ca9-22 oral cancer cells, Involving in cellular apoptosis, DNA damage and oxidative stress	(Yang *et al*., 2012)
Green algae	Dimethylsulfoniopropionate	Indicating anticancer activity in mice with Ehrlich ascites carcinoma	(Nakajima *et al*., 2008)
Laminaria japonica	Glycoproteins	Anticancer activity on human colon cancer cells	(Go *et al*., 2010)
Nizamuddinia zanardinii	Hydroperoxy sterol	Cytotoxicity in HT29, MCF7, A549, HepG2 and MDBK cell lines, positive result in terminal deoxynucleotidyl transferase dUTP Nick End labeling (TUNEL) assay	(Moghadam *et al*., 2013)
Sargassum filipendula	Heterofucans	Anti-proliferative effects on cervical, prostate and liver cancer cells	(Costa *et al*., 2011)
Sargassum horneri	Fucoidans	Anticancer activity on human colon cancer cells	(Ermakova *et al*., 2011)
Sargassum oligocystum	Aqueous extract	Inhibition of the proliferation of human leukemic cell lines	(Zandi *et al*., 2010a)

their metabolites which are recently published, have been reviewed here. Table 3 exhibits a collection of different anticancer metabolites recently isolated and identified from marine organisms.

Natural promising anticancer candidates under trials: Piperlongumine is a natural compound from the *Piper longum* (Piperaceae) introducing a potent anticancer medicine. This compound can bind to the active sites of some key cellular antioxidants such as glutathione S-transferase and carbonyl reductase-1. Piperlongumine cannot raise ROS in the normal cells (Burgess, 2011; Saeidnia and Abdollahi, 2013a). It is found that the activity of piperlongumine can be related to two mechanisms. The first one is to enhance in ROS in cancer cells, while in the second mechanism, it can be an inhibitor of the Ubiquitin-Proteasome System (UPS). When a tumor cell exposes to piperlongumine, the accumulation of a reporter substrate (rapidly degraded by the proteasome) and conjugated proteins occurs. Moreover, the researchers suggested that the inhibition of the UPS at a pre-proteasomal step is prior to deubiquitination of malfolded protein substrates at the proteasome and the induction of ROS might be a consequence of this inhibition (Jarvius *et al*., 2013).

Curcumin (Fig. 4) is another natural compound obtained from *Curcuma longa* (Zingiberaceae) which can be involved in alkylation of catalytic cysteine of DNA methyltransferase-1 DNMT1. This compound is well-known as an epigenetic modulator of miRNAs in cancer cell targeting. Curcumin is reported to directly induce a tumor-suppressive miRNA, named "miR-203" in bladder cancer. In fact, miR-203 is frequently down-regulated in bladder cancer due to DNA hypermethylation of its promoter. Curcumin can induce hypomethylation of the miR-203 promoter and subsequent up-regulation of miR-203 expression (Saini *et al*., 2011). On the other side, curcumin is a typical antioxidant phenolic compound playing role by oxidative coupling reaction on 3'-position with the lipids and consequently possible Diels-Alder reaction between two molecules. Meanwhile, various clinical trials for this anticancer natural compound have been undertaken until now and the efficacy of curcumin or other curcuminoids or turmeric products has been evaluated. For instance, the toxicology, pharmacokinetics and biologically effective dose of curcumin in patients with resected urinary bladder cancer, arsenic-associated Bowen disease of the skin, uterine Cervical Intraepithelial Neoplasm (CIN), oral leucoplakia and intestinal metaplasia of the stomach have been studied in a Phase 1 clinical trial. Furthermore, the results of three month administration of curcumin showed no toxicity by doses up to 8 g day^{-1}. The bulky volume of the drug was not acceptable to the patients (>8 g day^{-1}). The peak of serum concentration for curcumin was commonly found at 1 to 2 h after intake and gradually declined within 12 h but urinary excretion was not detectable. However, two patients developed frank malignancies in spite of curcumin treatment. Histologic improvement of precancerous lesions has been observed in one of two patients with resected bladder cancer, two of seven patients of oral leucoplakia, one of six patients of intestinal metaplasia of the stomach, one of four patients with CIN and two of six patients with Bowen disease. In

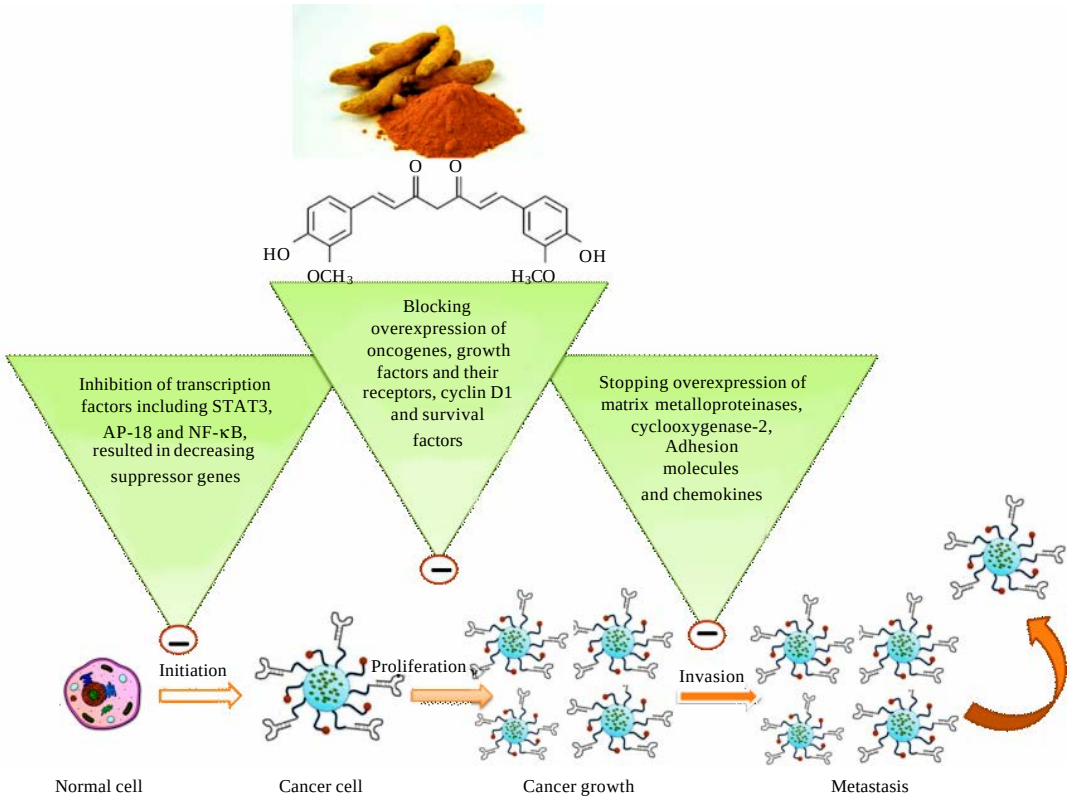

Fig. 4: Probable interference of curcumin in various stages of carcinogenesis, Activator Protein-18 (AP-18), Nuclear Factor kappa-B (NF-κB) and Signal Transducer and Activator of Transcription 3 (STAT3)

conclusion, the safety of curcumin (doses <8 g day^{-1}, orally for 3 months) has been demonstrated. This trial has also suggested the chemopreventive ability of this compound against cancerous lesions (Gupta *et al*., 2013). Additionally, as an example for phase II clinical trials, curcumin has been revealed safe and well-tolerated in patients with advanced pancreatic cancer (Dhillon *et al*., 2008). The problem with curcumin is its poor bioavailability due to poor absorption, rapid metabolism and rapid systemic elimination which affects its therapeutic efficacy (Anand *et al*., 2007). However, the bioavailability of curcumin has been greatly enhanced by reconstituting curcumin with the non-curcuminoid components of turmeric and also it is reported that the phospholipid formulation increased the absorption of demethoxylated curcuminoids much more than that of curcumin (Antony *et al*., 2008; Cuomo *et al*., 2011). The US FDA has approved curcumin as GRAS (generally recognized as safe). It is now being employed and marketed as a supplement in several pharmaceutical forms, including capsules, tablets, ointments etc. (Goel *et al*., 2008).

Genistein (an isoflavonoid usually find in *Genista tinctoria*) is one of the anticancer agents which can act *via* epigenetic mechanism by regulating miRNA and removing the Mini-Chromosome Maintenance (MCM) gene in prostate cancer cells and also suppressing MCM2 by inducing the upstream miRN A-1296 (Schneider-Stock *et al*., 2012). However, there is a concern on its antioxidant activity which is in controversy with its anticancer properties. As it is already discussed, genistein can enhance the antioxidant enzymes activity including catalase and SOD as well as glutathione peroxidase and reductase in various organs. Today, some modes of action have been found for genistein's anticancer effect. For instance, it can potentially inhibit estrogen activity and regulate gene expression. Furthermore, the epigenetic mechanism of anticancer for this compound is much less affected by its antioxidant properties compared to particular enzyme inhibition (Abdollahi and Shetab-Boushehri, 2012; Saeidnia and Abdollahi, 2013a; Watson, 2013).

Resveratrol (3,4',5-trihydroxystilbene) is a naturally occurring phytoalexin easily accessible in dietary

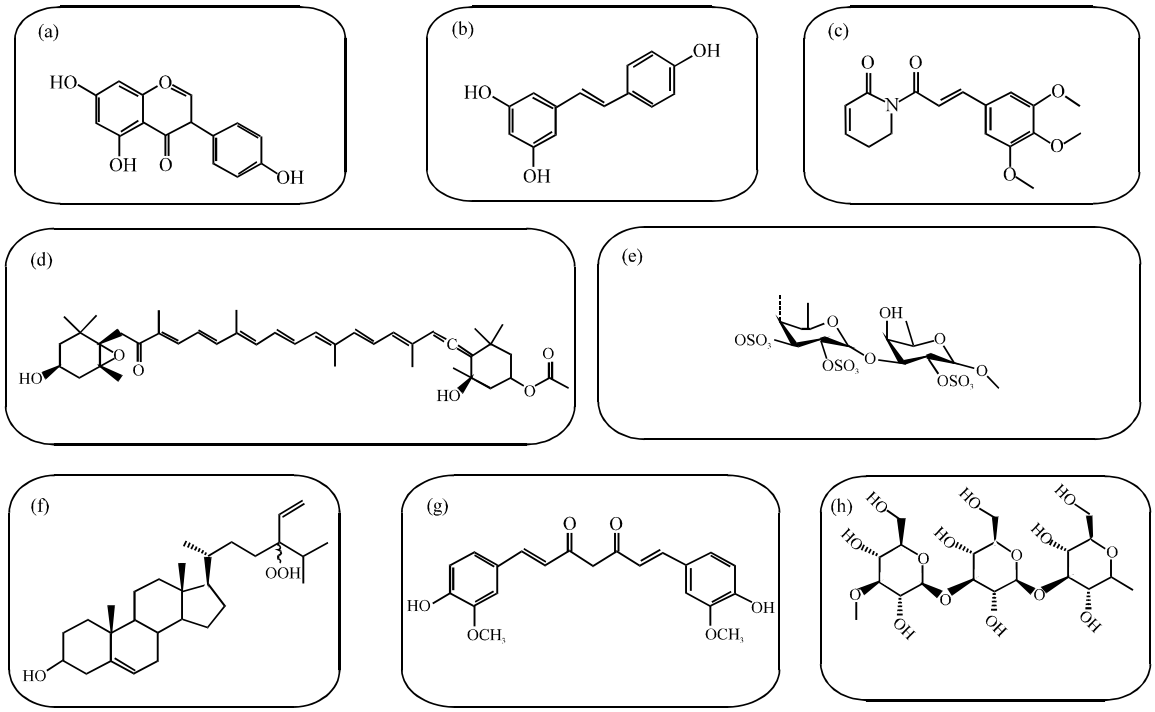

Fig. 5(a-h): Chemical structures of some important natural compounds with anti-neoplastic activity, (a) Genistein, (b) Resveratrol, (c) Piperlongumine, (d) Fucoxanthin, (e) Fucoidans (f) Hydroperoxy sterol, (g) Curcumin and (h) Glucans

vegetables and fruits (Chang *et al*., 2011; Wallerath *et al*., 2002). For the first time, resveratrol was identified as a bioactive compound in 1992. It is found in a variety of plants, especially in the red grapes. Actually, there is considerable trend to this compound as a potential cancer chemo-preventive agent due to its inhibitory activity on various pathways involved in carcinogenesis (Baur and Sinclair, 2006). Its structure shows similarity to diethylstilbestrol (DES) known as a phytoestrogen and previous studies showed that estradiol, DES and resveratrol could alter the FOF1-ATPase activity selectively with different mechanisms (Kipp and Ramirez, 2001). However, treatment of MCF-10F cells with DES, a known human carcinogen resulted in depurinating adducts involving in the induction of breast neoplasia. Literature reveals the ability of resveratrol to prevent the formation of estrogen-DNA adducts, thus preventing a key carcinogenic event (Hinrichs *et al*., 2011). However, the particular role of resveratrol as an estrogen agonist (or antagonist) remains to be elucidated. Tissue-specific expression of α and β estrogen cofactors, regulating DNA binding and different gene promoters, are important parameters to determine the exact role of resveratrol (Le Corre *et al*., 2005). To the best of our knowledge, resveratrol is well-documented to stop topoisomerase activity. Treatment of glioblastoma cells has been reported for resveratrol observed as a "topoisomerase poison" probably because of prolongation of the topoisomerase-DNA complex (Leone *et al*., 2010). Moreover, literature showed that resveratrol can inhibit telomerase activity in breast and colon cancer cells correlated with lowering nuclear levels of human telomerase reverse transcriptase (hTERT) (Fuggetta *et al*., 2006; Lanzilli *et al*., 2006). On the other hand, osteosarcoma and lung cancer therapeutic properties of resveratrol is associated with causing instable telomer, phosphorylating of histone H2AX (H2A histone family, member X) and p53 and activating DNA signaling (Rusin *et al*., 2009).

Literature demonstrated that ATF3 is a member of the ATF/CREB (cAMP response element binding) family of bZIP transcription factors and found as a stress inducible and/or adaptive response gene (Thompson *et al*., 2009). On the other side, there are several evidence demonstrating that ATF3 may act as a tumor inhibitor and mediator of apoptosis, at least in part, by ATF3 (Whitlock *et al*., 2011). The structures of some important natural compounds with anti-neoplastic activity are shown in Fig. 5.

HIGH THROUGHPUT SCREENINGS AND REVERSE PHARMACOLOGY

In order to facilitate the cancer drug discovery and developments, new strategies should be considered such as biotechnology approaches to help obtaining more effective or lead compounds from the natural sources. In addition, traditional screening of medicinal plants, marine algae or other natural resources is necessary to find effective compounds with lower toxicity and higher activity rather than present drugs. New approaches in this area have been created regarding new aspects of "reverse pharmacognosy" and its complementary "reverse pharmacology" which coupled the high throughput screening, virtual screening and *in silico* databases with traditional medicine knowledge. This has made possible to identify numerous *in vitro* active and selective hits which will enhance the speed of drug discovery from natural sources (Saeidnia and Gohari, 2012; Saeidnia *et al*., 2013). In fact, chemistry and high-throughput screening are combined and thus resulted in identification of numerous selective active compounds. But, the problem is that they have been evaluated *in vitro* not *in vivo*. Traditional treatments by use of natural medicines have been successful in many populations worldwide, representing various aspects of knowledge that are sometimes neglected in modern medicine due to differences in the concepts of disease. Actually, reverse pharmacognosy (from diverse molecules to plants) is a complementary to pharmacognosy (from biodiverse plants to molecules) and applies new techniques including virtual screening and a knowledge database containing the traditional uses of plants. The specialists in this area believe that integrating pharmacognosy and reverse pharmacognosy may provide an efficient and rapid tool for natural drug discovery (Do and Bernard, 2004). Alongside reverse pharmacognosy, reverse pharmacology is defined as a target-based drug discovery. However, this area covers screening of chemical libraries which can be employed to identify compounds that bind with high affinity to the target. The hits from these screens are then used as starting points for drug discovery (Swinney and Anthony, 2011).

BIOTECHNOLOGY: NEW APPROACH IN ANTICANCER DRUG DISCOVERY

Regarding the restrictions in production of secondary metabolites, biotechnology can offer an alternative method for more production of high quantitative natural metabolites or products in a relatively short time. Plant biotechnology comprises several techniques *in vitro*, since they allow manipulating the parameters influencing the growth and metabolism of cultured tissues. As a matter of fact, plant tissue culture fundamentally consists of inoculating an explant (that is a piece of plant tissue, such as a leaf or stem segment) from a donor plant on a medium containing nutrients and growth regulators and then causing the formation of a more or less dedifferentiated, rapidly growing callus tissue. The perspectives of plant cell culture in anticancer drug discovery are going to be highly interested, although the important plant-derived commercial anticancer drugs including *vinblastine* and *vincristine* are still obtained from cultivated *Catharanthus roseus*. On the other hand, some commercial anticancer drugs are semi-synthetically produced from natural metabolites as lead compounds which can be isolated from *in vivo* sources too. Now-a-days, there are only a few natural anticancer products that are being produced *via* methods of biotechnology including anhydrovinblastine from *Vinca rosea*, paclitaxel from *Taxus brevifolia*, podophyllotoxin from *Podophyllum hexandrum* and galactose binding lectin from *Viscum album*. However, these compounds are mostly produced in laboratories (Lata *et al*., 2009; Liu and Khosla, 2010; Ionkova, 2011).

NANOTECHNOLOGY: NOVEL AND STRONG TARGETED APPROACHES

Finding new targets is the main goal in drug discovery of cancer. Moreover, nanoparticles show a great promise in the treatment of a wide range of diseases due to their flexibility in structure, composition and properties. Nanoparticle targeting anticancer drugs especially those provided by use of poly (lactic-co-glycolic acid) (PLGA) have been recently more considered because of biodegradability, biocompatibility, surface modification, stability, excellent pharmacokinetic control and suitability for entrapping wide range of therapeutic agents but concerns on the possible toxicity of all nanocompounds still remain (Swinney and Anthony, 2011; Mostafalou *et al*., 2013). As an example, literature reveals that the inhibitory effect of rapamycin on the maturation of Dendritic Cells (DCs) regarding the phenotype, cytokine production and functional effects on the proliferation of T cells was significantly increased by PLGA delivery (Haddadi *et al*., 2008).

More recently, there has been an important focus on the field of cancer immunotherapy leading to the development of a safe and effective cancer vaccine formulation. Now-a-days, poly (d, l-lactic-co-glycolic acid) nanoparticles (PLGA-NPs) have been applied as the novel cancer vaccine delivery systems. Not only those

nanoparticles (contain antigens along with adjuvants) can target antigen actively to DCs but also activate the immunity and rescue impaired DCs from tumor-induced immuosupression (Hamdy *et al*., 2011c). Furthermore, the same investigators reported the efficacy of PLGA-based vaccine (PLGA nanoparticles co-encapsulating the poorly immunogenic melanoma antigen, tyrosinase-related protein 2 and Toll-like receptor ligand) in breaking immune-tolerance to cancer-associated self-antigens in mice bearing melanoma B16 tumors. The results demonstrated that the mentioned vaccine could induce therapeutic anti-tumor effect. Additionally, the potential of PLGA nanoparticles as competent carriers for future cancer vaccine formulations was supported (Hamdy *et al*., 2008).

CONCLUSION

Cancer occurs when alterations of genetic material create the abnormal status and activities leading to unregulated proliferation of cells in the body. However, cancer is one of the most predominant diseases causing death. Due to restrictions and side effects of the present chemotherapeutic and chemo-preventive antitumor drugs and also thousands of secondary metabolites formed in natural sources, there is a high trend toward novel drug discovery from nature. Beside the well-known anticancer plants, several fungi are found effective on various cancer cells and some of them may surpass the pre-clinical evaluations to become a promising candidate for clinical tests, of which *Ganoderma lucidum* is an important source of anti-proliferative and immunomodulatory components. Furthermore, marine organisms have been investigated and proven to be rich sources of extraordinary chemical structures, some of which possess a good anticancer activity. Until date, not only a minority of algae has been studied but also many species of them exhibited geographic variation in their chemical composition. Despite a rapid growth in the number of drugs available to treat cancer, it still remains a big concern in the world. Now-a-days, many patients intend to apply complementary or alternative therapies to manage their diseases while it is hard for healthcare practitioners to keep up with this evolving field. Additionally, when we focus on dietary supplements, the science behind the perceived benefits is not sufficient. Actually, broad spectrum of phytopharmaceuticals are available to practicing healthcare professionals which hold a great promise in the chemoprevention and chemotherapy of cancers (Saeidnia and Abdollahi, 2013a, b)

Regarding huge amount of costs paid each year for discovery and development of effective cancer drugs, there has been no sufficient progress in introducing novel effective treatments yet (Dickson and Gagnon, 2004). Many adverse effects of anticancer drugs are still an ongoing problem. Although all the scientists are not in agreement with beneficial usage of alternative therapies in cancer therapy, a number of natural products may lessen or at least ameliorate some cancers without causing the serious or significant adverse effects (Bagchi and Preuss, 2005). It seems that many vegetables, fruits, mushrooms, edible algae and also medicinal plants can be useful in life-improving, if not life-saving of cancer patients (Cho, 2011).

But there is an important concern regarding consumption of antioxidant containing supplements and/or herbal and/or natural products suggesting a serious need to revise the conventional anticancer drug discovery methods (Saeidnia and Abdollahi, 2013a; Watson, 2013). There are some strategies, in which researchers try to find out novel anticancer drugs within antioxidant compounds that are under question due to recent publications on how the antioxidants interfere with anticancer activity of chemotherapeutic drugs and lessen their efficacy (Abdollahi and Shetab-Boushehri, 2012; Shetab-Boushehri and Abdollahi, 2012). As we already described in other study, application of antioxidants during cancer treatment could diminish benefits of chemotherapy or radiation in the patients, by scavenging free radicals which destroy quick-dividing cancer cells. For this reason, the critical advice to patients treated by chemotherapy or radiation is not to take antioxidant supplements or not to be under treatment with herbal or natural medicines (even diets), in which high contents of antioxidants such as polyphenols, vitamin C and E exist (Shetab-Boushehri and Abdollahi, 2012). However, there is no doubt that some of the phenolic compounds such as resveratrol, genistein and also piperlongumine are potentially promising candidates for chemoprevention /chemotherapy of a varieties of cancer. Some of these compounds have been studied in both *in vivo* and clinical trials that are described in the present review. Although, these compounds possess antioxidant activity, they can act via various mechanisms. Some of those mechanisms (like epigenetic mode of action) are less impacted by their antioxidative effects.

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