



ANTICANCER ACTIVITY OF NATURAL COMPOUNDS

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ABSTRACT

Cancer is one of the leading causes of death in both developed and developing countries in the world. It is an abnormal growth of cells in the body that can lead to death. The number of cases of cancer begins with mutations in DNA, which instruct the cells to grow and divide. Normal cells possess the DNA repair mechanism, but lacking this due to DNA mutations lead cells to grow and become cancerous (Hosseini, 2015). With the development of science, various treatment methods for cancer have been discovered. Among these treatment methods, chemotherapy, an accepted treatment method also carries some harmful effects. Intern, according to research diverse natural organisms including plants and microorganisms derived natural compounds have proved to be effective and safe as a treatment and management of cancer (Distefano, 2015). In the modern world most of the research work on cancer, based on plants and natural compounds derived therapeutic drugs and treatment methods. As a result, many natural compounds and their analogues have been identified as potent anti-cancer agents. Further, with emerging research and technology new anticancer properties of various natural products are being identified. Even though, there are several medicines available in the market to treat various types of cancer but no drug is found to be fully effective and safe (Salim, Chin and Kinghorn, 2008; Distefano, 2015).

Key words: Cancer, Anticancer activity, Natural compounds, Cancer treatments

INTRODUCTION

Cancer is an abnormal growth and uncontrolled division of cells in tissues and organs which can lead to death. It is a major hazard to human health and affects the lives of millions of people in the world (Jayarathna *et al.*, 2016; Kaur *et al.*, 2011). Further, cancer is considered to be the second leading cause of death in the world after cardiovascular disease. (Fridlender, Kapulnik and Koltai, 2015). There are various types of cancer found in humans all-around the world and most of them have been discussed in detail in the medical literature. According to World Health Organization (WHO) the most common types of cancers are lung cancer, colorectal cancer and breast cancer (Nobili *et al.*, 2009). The cause of cancer can be smoking, chronic inflammation, hormone imbalance, chronic infection, and dietary imbalance, etc. Further, it can also due to a combination of genetic and non-genetic changes induced by environmental factors that give rise to incorrect activation of specific genes leading to neoplastic transformation (Jayarathna *et al.*, 2016).

One of the main reasons for spending lot of manpower, materials, and resources on researching and developing new drugs for treating of cancer is due to the harmful effects on human body by current treatment methods such as chemotherapy and various other cancer treatment methods (Zhouet *al.*, 2014). Since cancer cells have increased drug resistance, the researchers have to develop new anti- cancer drugs and therapies for the increasing demand. Based on research various compounds derived from natural sources including plants and microorganisms proved to have increased anticancer activity (Dai *et al.*, 2016).

Medicinal plants maintain the health and vitality of individuals and also cure various diseases including cancer without causing toxicity. Therefore, natural products discovered from medicinal plants have played an important role in treatment of cancer (Nobili *et al.*, 2009). Dietary phytochemicals which are derived from plants have been used for the treatment of cancer throughout history due to their safety, low toxicity, and general availability. Promising phytochemicals not only disrupt aberrant signaling pathways leading to cancer but also synergize with chemotherapy and radiotherapy. Thus, the cancer chemoprevention and therapeutic potential of naturally occurring phytochemicals are of great interest (González-Vallinas *et al.*, 2013).

Cancer therapeutic drugs are manufactured from plant matrices such as leaves, woods, fibers, and storage parts of plants (fruits, vegetables, tubes). The chemical compounds from these plant materials which derived biosynthetically from plant's primary metabolites are used for manufacturing anti- cancer agents. As examples carbohydrate, amino acids and lipid compounds. (Salim, Chin and Kinghorn, 2008). These chemicals termed phytochemicals, can be classified into several groups according to their chemical structure. A variety of anti- cancer herbs and plants have been identified in the world, especially from regions like Africa and Asia. Further, some natural products isolated from microorganisms such as bacteria and fungi have aided in the identification of diverse molecules and led to the discovery of several important anti-cancer drugs. (Singh *et al.*, 2016).

The development of anti- cancer therapeutic drug discovery is by molecular modeling combining with chemistry and synthetic chemistry methods. Compounds which are derived from natural products provide a valuable source of modern medicines for human. The secondary metabolites of plants can be use directly in their original forms as drugs or as drug precursors, templates for synthetic modifications and as pharmacological probes (Salim, Chin and Kinghorn, 2008).

NATURAL PRODUCTS IN ANTICANCER THERAPY

Natural products have been used for the treatments of cancer due to their less toxic side effects compared to treatments such as chemotherapy and surgeries. It is believed that more than 50% of drugs are derived from natural products which can control cancer cells (Kaur *et al.*, 2011; Pratheeshkumar *et al.*, 2015). Number of natural compounds derived from plants, animals, and microbes which are in their secondary metabolites state have been developed into drugs to treat cancer (Hosseini, 2015). Development of drugs using natural products started with the development of pharmacological experiment technology, modifications, and transformation of natural products with the help of modern extraction, modification, and transformation technologies (Zhouet *al.*, 2014; Dai *et al.*, 2016).

IDENTIFICATION OF PLANTS WITH ANTI- CANCER PROPERTY

Most of the plants having medicinal properties or anti- cancer activity are categorized as medicinal or herbal plants. Therefore, the identification of anti- cancer compounds in plants are majorly based on the predicted medicinal plants. These compounds can identify frequently in the plant families such as Araliaceae, Asteraceae, Boraginaceae, Ranunculaceae and Rosaceae (Dai *et al.*, 2016). Biologically active natural compounds such as curcumin, resveratrol, cucurbitacins, isoflavones, saponins, phytosterols etc have been isolated from plants (Nobili *et al.*, 2009; Distefano, 2015).

Natural compounds have been used since last 200 years as treatments for various diseases. A variety of anti- cancer herbs and plants have been identified in the world, especially from regions like Africa and Asia. Following table conclude some of these plants having anti-cancer property (Zhouet *al.*, 2014).

Table 1: Plantshaving anti-cancer properties

Plant/ family and place of deposition	Part of the plant and family
<i>Camptosperma zeylanica</i>	Leaves and Bark
<i>Vateria copallifera</i>	Leaves and Bark
<i>Diphylleia sinensis</i>	Berberidaceae
<i>Arnebia guttata</i>	Boraginaceae
<i>Cimicifuga foetida</i>	Ranunculaceae
<i>Sanguisorba officinalis</i>	Rosaceae
<i>Gynostemma pentaphyllum</i>	Cucurbitaceae
<i>Platycodon grandiflorum</i>	Campanulaceae
<i>Panax notoginseng</i>	Araliaceae
<i>Agapanthus africanus</i>	Amaryllidaceae
<i>Aglaia sylvestre</i>	Meliaceae
<i>Ailanthus altissima</i>	Simaroubaceae
<i>Veratrum californicum</i>	Melanthiaceae
<i>Petroselinum crispum</i>	Leaves and Roots
<i>Podophyllum hexandrum</i>	Leaves and Flower
<i>Moringa peregrina</i>	Seeds
<i>Curcuma longa</i>	Roots
<i>Crocus sativus</i>	Flowers and Anther
<i>Vitis vinifera</i>	Fruits
<i>Brassica oleracea</i>	Brassicaceae
<i>Camellia sinensis</i>	Leaves
<i>Zingiber officinale</i>	Roots
<i>Sophora flavescens Ait</i>	Leaves
<i>Catharanthus roseus</i>	Apocynaceae
<i>Podophyllum emodi</i>	Roots
<i>Scutellaria baicalensis</i>	Roots and Leaves
<i>Acacia catechu</i>	Wood
<i>Amoora rohituka</i>	Leaves
<i>Dysoxylum binectariferum</i>	Leaves

<i>Andrographis paniculata</i>	Leaves
<i>Cephalotaxus harringtonia</i>	Seeds
<i>Tabebuia avellanedae</i>	Bark
<i>Gloriosa superba</i>	Leaves and Roots
<i>kirilowii maximowicz</i>	Roots
<i>Prunus africana</i>	Bark and Seeds

(Jayarathna *et al.*, 2016; Dai *et al.*, 2016; Kaur *et al.*, 2011; Oh *et al.*, 2016; Distefano, 2015; Russo *et al.*, 2010; Ochwang, Kimwele and Oduma, 2016; Poonam and Chandana, 2015; Nobili *et al.*, 2009; Simon and Jayakumar, 2016; Komakech *et al.*, 2017)

Major plant – derived natural products as anti - cancer drugs.

There are numerous types of plants that produce various types of natural compounds which can be used as drugs for anti-cancer therapy. These different types of plants and herbs are specific for a group of natural compounds. As an example, *Gloriosa superba* contain a large amount of alkaloid components such as colchicine and gloriosine (Simon and Jayakumar, 2016). By using different biomedical techniques, these natural compounds specific for anti- cancer activity can be extracted from plant materials (Zhou *et al.*, 2014; Jayarathna *et al.*, 2016).

Some of the natural compounds specific for anti- cancer activity are Alkaloids, Taxane and podophyllotoxin, Flavonoids, Polysaccharide, polyphenols, brassinosteroids, polyphenols, organosulfur compounds, phytosterols (Zhou *et al.*, 2014; Hosseini, 2015).

Alkaloids

Alkaloids are an organic compound containing nitrogen which present in natural compounds having anti- cancer activity. Alkaloids act as a potent broad spectrum anti-cancer agent by inhibiting and reducing the circulating glucocorticoid levels and reducing the tumor activity (Ochwang, Kimwele and Oduma, 2016). The natural compounds extracted from *Sophora flavescens* Ait demonstrated anti-cancer effect in a number of cancer cells including lung, breast etc. The type of alkaloids which can extract from *Sophora flavescens* Ait can inhibit the growth of cancer cells by inhibiting proliferation and further inducing apoptosis in Acute myeloid leukemia (AML) by influencing the mitochondrial membrane potential (Zhou *et al.*, 2014; Oh *et al.*, 2016; Nobili *et al.*, 2009).

Podophyllotoxin

Podophyllotoxins are the natural compounds which can be extracted from plants such as *Podophyllum peltatum* and *Podophyllum emodi* having a long history for treating skin cancers (Poonam and Chandana, 2015). Podophyllotoxin have serious side effects because of their poor cytotoxic selectivity but also carries potent anti- tumor activity. In spite of this limited effectiveness of podophyllotoxin in anti- cancer therapy, several anti-cancer drugs have been derived from this natural compound against several malignant conditions including lung cancer, breast cancer, ovarian cancer, and prostate cancer (Singh, Dhanalakshmi and Agarwal, 2002). The podophyllotoxin produce the effect against cancer by breaking down the microtubule function leading to block mitosis and formation of the cancer cells (Zhou *et al.*, 2014).

Flavonoids

Flavonoids are natural compounds having anti- cancer activity and it includes compounds such as isoflavones, flavonols, flavones, anthocyanidins, catechins, flavanones, and etc. These natural compounds can extract from plants such as *Scutellaria baicalensis* and *Acacia catech* (Salim, Chin and Kinghorn, 2008). Anti- cancer activity of the flavonoid compounds are by inhibiting the proliferation in several types of tumor cells and by inducing apoptosis in cancerous cells (de Melo *et al.*, 2011; Zhouet *al.*, 2014). Further, the type of flavonoids having the chemical structure similar to estrogen is called isoflavones which can be extracted from leguminous plants and has the ability to induce apoptosis in chemo- resistant cancer cells (Pratheeshkumar *et al.*, 2015).

Saponins

Plants and plant materials such as, sapindus fruits, mojave yucca roots, soapwort roots contain saponins. Mainly saponins has both anti- cancer and anti- inflammatory effects. Saponins demonstrate anti- cancer activity by anti- proliferation, anti- metastasis, anti- angiogenesis effects and reversal of multidrug resistance effects (Xu *et al.*, 2016).

Mostly saponins are ginsenoside which is a main extract from ginseng. Ginsenoside is a kind of triterpenoid saponins and main active ingredients in ginseng. Ginsenoside has higher anti- tumor activity without toxic side effects on normal cells. Further, ginsenoside has synergistic effects with chemotherapy and other drugs such as cisplatin. Ginsenoside regulates the proliferation of tumor cells, inducing differentiation and apoptosis of cells to exert anti-tumor effects (Zhouet *al.*, 2014).

Polysaccharides

Polysaccharides are also an important natural compound found in plant sources which play an anti-cancer role by a variety of approaches including regulation of immune system, by regulating phagocytic function of the reticuloendothelial system, improving the natural killer (NK) cell activity, activating macrophages, inducing the expression of immune-regulatory factors, affecting cell metabolism, inhibiting tumor cell cycle, and the activity of Superoxide dismutases SOD in tumor tissues (Marmot, 2006; Singh *et al.*, 2016; Zhouet *al.*, 2014).

Following are some examples for other kinds of minor anti-cancer natural compounds; combretastatin A4, flavopiridol, homoharringtonine, andrographolide, sesquiterpene lactones, 27-KDA trichosanthin and β - lapachone.

Combretastatin A4 (CA 4).

Combretastatin A4 is a type of flavopiridol derived from various plant species. Majorly combretastatin A4 is isolated from the leaves and stems of *Amoora rohituka* and *Dysoxylum binectariferum*. Combretastatin act as a potent microtubule targeting and vascular damaging agent in cancer cells. CA4 retain anti- proliferative and pro- apoptotic activity in higher doses (Nobili *et al.*, 2009; Oh *et al.*, 2016).

Flavopiridol

Flavopiridol is an important type of natural compound extracted from plants and an effective cycling dependent kinase inhibitor due to its direct action of binding to ATP (Nobili *et al.*, 2009). Flavopiridol is a potent apoptotic agent by its ability to cause cell death in cycling and non-

cycling cancer cells by down regulating important cell survival proteins through inhibition of phosphorylation (Dai *et al.*, 2016).

Homoharringtonine

Homoharringtonine is an alkaloid which can extract from *Cephalotaxus harringtonia* seeds. Homoharringtonine (HHT) use as a tyrosine kinase inhibitor in non-small lung cancer cells. HHT causes cell apoptosis through the mitochondrial pathways and can inhibit cell growth, cell viability, and colony formation. The principle mechanism of HHT in inhibiting the produced new non- small lung cancer cells are by inhibiting protein synthesis and blocking cell cycle progression (Nobili *et al.*, 2009; Singh, Dhanalakshmi and Agarwal, 2002).

Andrographolide

Andrographolide is a diterpenoid lactone isolated from plants such as *Andrographis paniculata*. This natural compound can inhibit breast cancer cell proliferation, migration, and arrest cell cycle at G2/M phase. It can act as an effective anti - cancer agent by inducing apoptosis through caspase independent pathway in treatment for breast cancer (Nobili *et al.*, 2009; Poonam and Chandana, 2015).

Sesquiterpene lactones

Sesquiterpene lactones is a secondary metabolic natural compound of plants and has an anti-cancer effect by inhibiting the growth of tumor promoter- induced cells (Zhouet *al.*, 2014; Singh *et al.*, 2016).

β- lapachone

β- lapachone is a type of quinone extract from the bark of the *Tabebuia avellanedae*. β- lapachone act as an anti-cancer agent by inhibiting DNA topoisomerase I which can induced the cell cycle delay at G1 and S phase and apoptotic or necrotic cell death in variety of human carcinoma cells such as ovary cancer cells, colon cancer cells, lung, and prostate cancer cells (Nobili *et al.*, 2009; Russo *et al.*, 2010).

27- KDA trichosanthin

27- KDA trichosanthin is a protein found in *Trichosanthes kirilowii maximowicz* and responsible for ribosomal inactivation. Trichosanthin can inhibit the cell growth of diverse cancers by inducing anti-proliferative and apoptotic effects. (Zhouet *al.*, 2014; de Melo *et al.*, 2011)

Apigenin

Apigenin is a natural compound found in plants such as *Petroselinum crispum*, and *Moringa peregrine*. It is a type of flavonoid which can be metabolically activated to produce toxic prooxidant phenoxyl radicals. Therefore, apigenin used as a protein kinase inhibitor for effects on human breast cancer. Further, apigenin demonstrates a cytotoxic activity against breast cancer cell lines and act as a mediator for chemoprevention in the cancerous process (Pratheeshkumar *et al.*, 2015; Singh, Dhanalakshmi and Agarwal, 2002).

Curcumin

Anti- cancer effect of *Curcuma longa* (turmeric) have been identified against colon cancer, breast cancer, and brain tumor. Curcumin which can be found in turmeric can induce apoptosis in cancer cells without been cytotoxic to healthy cells (Distefano, 2015).

Crocetin

Saffron can be found in flowers and food colorant of Saffron sativus or Saffron crocus (*Crocus sativus*). Crocetin, an important constituent of saffron is used as a potential agent for novel anti-cancer drugs against pancreatic cancer, lung cancer, and colorectal cancer. The mechanism of action of saffron is still not that clear. But it is found that saffron is effective against the growth of cancer cells by inhibiting nucleic acid synthesis, enhancing anti-oxidative system, inducing apoptosis and hindering signaling pathways (Distefano, 2015; González-Vallinas *et al.*, 2013).

Cyanidins

Cyanidins can be found in grapes (*Vitis vinifera*), and also in red berries, apples, plums, red cabbage and red onions. Having antioxidants and Cyanidins in these, can reduce the risk of cancer by inhibiting cell proliferation and gene expression in colon cancer cells (Distefano, 2015).

Diindolylmethane (DIM) /Indole-3-carbinol (I3C)

Diindolylmethane (DIM) and Indole-3-carbinol (I3C) is found in Brassica vegetables, such as *Brassica oleracea var. italica*, and *Brassica oleracea var. botrytis*. Indole-3-carbinol is an important cancer prevention therapy for tobacco smoke carcinogen induced lung cancer prevention. The prevention occurs by affecting the modulation of receptor tyrosine kinase signaling pathway. Diindolylmethane has demonstrated exceptional anti-cancer effects against hormone responsive cancers like breast, prostate and ovarian cancers (Distefano, 2015; González-Vallinas *et al.*, 2013; Ochwang, Kimwele and Oduma, 2016).

Epigallocatechin gallate

Epigallocatechin gallate (EGCG) is an important natural compound found in green tea (*Camellia sinensis*) and shows beneficial effects in treating brain, prostate, cervical and bladder cancers. EGCG binds and inhibits the anti-apoptotic proteins in survived cells of both normal and cancer cells (Poonam and Chandana, 2015; Zhou *et al.*, 2014).

Gingerol

Gingerol is an important natural compound that can be extracted from ginger (*Zingiber officinale*) roots which shows an anti-cancer effect for colon, breast, ovarian and pancreatic cancers. Gingerol can destroy cancer cells by antioxidant, anti-inflammation, and anti-tumor promoting properties (Distefano, 2015).

IDENTIFICATION OF NATURAL COMPOUNDS WITH ANTI-CANCER PROPERTIES DERIVED FROM MICROORGANISMS

Natural products which are derived especially from microorganisms have served as a valuable source of diverse molecules in many drug discovery research and also led to the findings of several important anti-cancer drugs. The biologically active bio-molecules from microorganisms are purified by the microbial strains (Treasathomas *et al.*, 2011).

The extraction of identified bioactive molecules can be extracellularly or intracellularly from bacterial and fungal isolates that are grown under unusual conditions such as high temperature, high salt and various sugar concentrations. Further, these compounds are tested for cytotoxic potential on various cancer cell lines. Nuclear staining and flow cytometric studies have carried

out to assess the potential of the extracts in arresting the cell cycle. Further, biochemical tests and preliminary chemical investigations are conducted on each extract (Treasathomas *et al.*, 2011).

Marine microorganisms are a rich source of bioactive molecules with potential applications in medicine. Bioactive compounds which are isolated from marine organisms are screened for anti-cancer activity. Natural compounds such as malformin A, kuanoniamine D, hymenialdisine, and gallic acid extracted from marine organisms have shown higher anti-cancer activity. Therefore, different concentrations of various extracts such as, soft coral *Sarcophyton sp* extracts are tested against different cancer cell lines (Oh *et al.*, 2016). Treatments with these natural compounds have shown cancer cell death with the presence of nuclear fragmentation, membrane protrusion, blebbing and chromatin segregation at the nuclear membrane, which shows typical characteristics of cell death by apoptosis (Treasathomas *et al.*, 2011).

STRUCTURAL MODIFICATION OF NATURAL COMPOUNDS

The huge structural diversity of natural compounds have been described according to their bioactivity. Several natural compounds isolated from plants, microorganisms, marine flora, and fauna can serve as lead compounds (Bhargavi and Jayamadhuri, 2016; Treasathomas *et al.*, 2011). Further, their therapeutic potential is improved by molecular modifications such as semisynthetic processes of new compounds obtained by molecular modification of functional groups of the lead compounds. With these modifications, natural compounds can generate structural analogues with higher pharmacological activity and with fewer side effects (Nobili *et al.*, 2009).

The process of molecular modification of natural compounds complement with high-throughput screening protocols, combinatorial chemistry, computational chemistry and bioinformatics. These screening protocols, techniques with combinatorial biosynthesis can provide new and effective compounds which can be used in clinical practice. (Nobili *et al.*, 2009).

CONCLUSION

An array of research have been conducted to search anticancer drugs derived from natural products. This is mainly due to its strong activity, high selectivity, low side effects and a wide range of anti-cancer activity. This resulted in finding a variety of natural compounds with cancer prevention activity (Kaur *et al.*, 2011; Zhou *et al.*, 2014). There are several plants and microorganisms derived compounds used as drugs for treating cancer (Nobili *et al.*, 2009; Oh *et al.*, 2016). Dietary phytochemicals which are derived from plants have been used for the treatment of cancer throughout the history due to their safety, low toxicity, and general availability. Promising phytochemicals not only disrupt aberrant signaling pathways leading to cancer but also synergize with chemotherapy and radiotherapy. Thus, cancer prevention and therapeutic potential of naturally occurring phytochemicals are of great interest (González-Vallinas *et al.*, 2013). Further, natural products derived especially from microorganisms have served as a valuable source of diverse molecules in many drug discovery research and led to the discovery of several important drugs (Treasathomas *et al.*, 2011). Other cancer treatment methods such as surgical removal, chemotherapy, radiation have severe side effects such as high toxicity. Therefore, to avoid these kind of disadvantages and circumstances, the use of naturally derived cancer therapeutic drugs are very important. (Fridlender, Kapulnik and Koltai, 2015; Singh, Dhanalakshmi and Agarwal, 2002)

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