Cancer Combating Biomolecules From Plants

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Abstract

Nature has been a source of medicinal products for many years, with many useful drugs developed from plant sources. Plant-based systems continue to play an essential role in healthcare, and their use by different cultures has been extensively documented. Several secondary metabolites from plant sources have proved to be an excellent reservoir of new medical compounds. Many anti-cancer agents have been isolated from various plant sources. Attempts to explore new anti-cancer and other medical compounds from natural sources are progressing in various laboratories. This chapter outlines the process of carcinogenesis potential anti-cancer agents, ayurvedic concept of carcinogenesis, the 'thridoshas', the correction methods, databases of naturally occurring anti-cancer agents, chemotherapeutic and chemoprotective activities of the compounds and their molecular targets. Curcuminoids, boswellic acid, polyphenols like catechin, procyanidins, camptothecin, cannabinoids, resveratrol, diallyl disulphide, combrestatin, ashwagandha, tanshinones, polygala, and ayurvedic formulations are among the ones discussed.

Keywords

Carcinogenesis • Ayurveda • Plant-based anti-cancer compounds

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8.1 Introduction

Carcinogenesis is the conversion of normal cells to cancerous cells through many stages, which happen over many years or even decades. In the initiation stage of carcinogenesis the carcinogens react with the DNA of the cells, and blocking this stage (onset) of cancer is an important approach in cancer prevention or treatment. Promotion, the second stage of cancer, may arise slowly over a long period of time, ranging from several months to years. The third stage is the progressive stage, involving the spread of the cancer. During the initiation and promotion stages of cancer, a change in lifestyle and diet could possibly prevent development of cancer. During the progressive stage, protective factors such as diet or lifestyle do not have much impact (Reddy et al. 2003). Garlic, ginger, soya, curcumin, onion, tomatoes, cruciferous vegetables, chillies, and green tea provide protection against cancer.

According to the International Agency for Research on Cancer (IARC), in 2012 "there were 14.1 million new cancer cases, 8.2 million cancer deaths and 32.6 million people living with cancer (within 5 years of diagnosis) worldwide. 57% (8 million) of new cancer cases, 65% (5.3 million) of the cancer deaths and 48% (15.6 million) of the 5-year prevalent cancer cases occurred in the less developed regions. In India, 1.02 million new cancer cases, 0.7 million cancer deaths and 1.8 million people living with cancer (within 5 years of diagnosis) in 2012" (http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx).

In spite of the amount of money in billions being spent on cancer research and the availability of the best health care in the world, there is high incidence of cancer in the United States. Lifestyle seems to be one major contributing factor to cancer, evident from the high incidence of cancer among immigrants from the East to the West (Kolonel et al. 2004a).

Carcinogenesis begins with cellular transformation, progresses to hyperproliferation and inflammatory processes, and finally leads to angiogenesis and metastasis. It is a three-phase process, which includes initiation, promotion, and progression of the tumour (Berenblum 1982). Oxidative damage to DNA, proteins, and lipids, resulting from an increase in oxidative stress, is considered to be one of the most important mechanisms contributing to the development of cancer. Since cancer is a multi-step process, the preventative action of phytochemicals may result from their additive or synergistic effects. A number of mechanisms exist by which phytochemicals aid in the prevention of cancer and they may include:

(i) Anti-oxidant and free radical scavenging activity
(ii) Induction of apoptosis
(iii) Anti-proliferative activity
(iv) Cell-cycle arresting activity
(v) Enzyme inhibition
(vi) Gene regulation (Liu 2004)

The search for potential anti-cancer agents from natural products dates back to 1550 BC. Scientific research reports only started emerging in the 1960s, with

Table 1 Some anti-cancer/cytotoxic drugs developed from plant sources

Therapeutic agent/Chemical compound	Plant source	Type of cancer	References
Vinblastine, vincristine (alkaloids)	*Catharanthus roseus*	Hodgkin's disease	Mans et al. (2000)
Etoposide, teniposide (epipodophyllotoxin)	*Podophyllum peltatum*	Testicular cancer, and small cell lung carcinoma, leukemias, Lymphomas	Lee (1999) Mans et al. (2000)
Paclitaxel, docetaxel (taxanes)	*Taxus brevifolia*	Ovarian and breast carcinoma	Mans et al. (2000)
Irinotecan, topotecan, 9-aminocampothecin, 9-nitrocampothecin (alkaloids)	*Camptotheca acuminata*	Advanced colorectal cancer, also active in lung, cervix and ovarian cancer	Srivastava et al. (2005)
Homoharingtonine (alkaloids)	*Harringtonia cephalotaxus*	Various leukemias	Mans et al. (2000)
4-Ipomeanol (Pneumotoxic furan derivative)	*Ipomoea batatas*	Lung cancer	Mans et al. (2000)
Salograviolide A (sesquiterpene)	*Centaurea ainetensis*	Colon cancer	Salla et al. (2013)
Iso-eco-tanapartholide (sesquiterpene)	*Achillea falcata*	Colon cancer	Salla et al. (2013)
Betulinic acid (tri-terpene)	*Ziziphus mauritiana*.	Human melanoma	Pisha et al. (1995)
Pervilleine A (tropane alkaloid)	*Erythroxylum pervillei*	Oral cancer	Silva et al. (2001)
Sylvesterol	*Aglaia foveolata* Pannell	Prostrate cancer	Hwang et al. (2004)

investigations by Hartwell and colleagues (Pettit 1995), on the anti-cancer effect of podophyllotoxin and its derivatives. The biological and chemical diversity among natural resources promotes the discovery of novel compounds. Administration of these compounds, especially in combination with synthetic agents leads to the management and cure of human cancer. Nearly 75% of the medications being prescribed for use in cancer treatment are sourced from plants (Table 1) and approximately 74% of these were discovered from the traditional claims (Shishodia and Aggarwal 2004).

The phytochemicals that offer protection against cancer are "curcumin, genistein, resveratrol, diallyl sulfide, (S)-allyl cystein, allicin, lycopene, ellagic acid, ursolic acid, catechins, eugenol, isoeugenol, isoflavones, protease inhibitors, saponins, phytosterols, vitamin C, lutein, folic acid, beta carotene, vitamin E and flavonoids, to name but a few" (Reddy et al. 2003).

Modern day medicine uses few plant products in cancer therapy, taxol and vinca alkaloids, to name a few. Out of the 121 drugs currently in vogue for cancer therapy 90 are plant derived (Craig 1997, 1999). According to Newman et al. (2003) 48 out of 65 drugs approved for cancer treatment during a period between 1981 and 2002, were based on natural products, or mimicked natural products in one form or another. These phytochemicals, which combat disease by preventing inflammatory response, are commonly called chemotherapeutic or chemo-preventive agents.

8.2 Ayurvedic Concept of Carcinogenesis

The balanced condition of *Vata*, *Pitta*, and *Kapha* ('Thridoshas- three humors') in body, mind, and consciousness is the ayurvedic concept of health. Ayurvedic treatment restores the balance between these three systems. Charaka and Sushruta, in their compilations or "samhitas", use the terms *Granthi* and *Arbuda* for benign tumour and malignant tumour respectively (Charaka 700 BC; Susrutha 700 BC). Tumours become malignant when all three "doshas" lose mutual co-ordination, causing morbidity (Singh 2002). Several reports suggest that ayurvedic plants and their constituents have modulating effects on several therapeutic targets. However, ayurvedic drugs are yet to be validated by current scientific procedures (Aggarwal et al. 2006).

The ayurvedic approach to treatment of cancer including *Sodhana chikitsa* (detoxification) is the prime method for medical management of cancer. Internal and external purification processes include five ways of treatment, collectively named *Panchakarma chikitsa*. *Samana chikitsa* (palliative treatment) is to rectify the dosha and to cure the disease. Rejuvenative therapies restore and strengthen the patient and remove any ill effects that may have occured due to purification or cleansing. This is the step prior to therapy specific to the disease (Balachandran and Govindarajan 2005).

There are numerous pre-clinical studies with individual herbs and their derivatives and a few reports on complex herbal formulations like *Rasagenthi lehyam, Brahma rasayana*, *Semecarpus lehyam*, and *Triphala*, etc. (Joseph et al. 1999; Rekha et al. 2001; Jena et al. 2003; Naik et al. 2005).

Cancer is a highly complex disease developed over a period of 20–30 years or more, before it can be detected. Interruption of a cell-signalling pathway has been the method of cancer treatment in most cases, but multi-targeted therapy may have better chances of success. Current treatment methods for cancer concentrate at the molecular level rather than organism level (Reductionist approach). On the other hand, ayurvedic treatment for cancer is holistic, which may be preferred (Garodia et al. 2007).

8.3 Anti-tumour Phytoconstituents

The anti-tumour activity of curcumin is manifold and research evidence accumulated over the last 50 years indicates that curcumin prevents and cures cancer. The anti-cancer property of curcumin is via its ability to suppress the proliferation of a variety of tumours. Curcumin inhibits carcinogenesis of the breast, colon, liver, lung, skin, stomach, etc. and the proliferation of a wide variety of malignant cells in culture. It also promotes apoptosis by way of caspase-9 activation, cytochrome c release, caspase-3 activation, inhibition of IkappaBalpha kinase, and so on (Mukhopadhyay et al. 2001; Anto et al. 2002; Aggarwal et al. 2003, Siwak et al. 2005; Yan et al. 2005; Aggarwal et al. 2005, Bachmeier et al. 2008, 2010). John et al. (2002) found copper complexes and its derivatives to be better anti-cancer agents than the original compounds. Karikar et al. (2007) reported the cancer-related application of "nanocurcumin" (<100 nm) on pancreatic cell lines. Pre-clinical studies on the anti-cancer property of liposome-bound curcumin formulation when compared to oxaliplatin (a standard chemotherapeutic agent for colorectal cancer) showed significant apoptotic effects in vitro and in vivo (Li et al. 2007).

Jančinová et al. (2011) found that curcumin (diferuloylmethane) not only suppressed mechanisms leading to inflammation, but also resolved inflammation by apoptosis of neutrophils. Curcumin decreased phagocytotic potential in neutrophils, both in vitro and in vivo when orally administered.

Boswellic acid, the active component of *Boswellia serrata*, inhibited 5-LOX and leukocyte elastase, thereby reducing inflammation (Safayhi et al. 1992, 1994, 1995; Ammon et al. 1993; Kapil and Moza 1992). Acetyl-keto-beta-boswellic acid (AKBA), an active principle from *B. serrata*, was found to combat inflammatory diseases, including cancer. AKBA inhibits cancers of brain, colon, liver, pancreas, blood, etc. (Shao et al. 1998; Glaser et al. 1999; Jing et al. 1999; Huang et al. 2000; Winking et al. 2000; Liu et al. 2002; Zhao et al. 2003; Park et al. 2011). Neeta and Dureja (2014) highlighted the modalities of treatment, the structure, and the toxicological profiles of the different *Boswellia* species. Yadav et al. (2012) reports boswellic acid analogue to prevent proliferation and spread of colorectal cancer of humans in vivo using nude mice models.

Molecular targets of biomolecules from ayurvedic plants include nuclear factor kB acted upon by a wide range of plant-derived molecules like those from *Curcuma longa* (more than 32), *Withania somnifera*, *Boswellia serrata*, *Zingiber zerumbet*, etc.; transcription activators (STAT) -3, Nrf-2; targeted by *C. longa*, *Indigofera tinctoria*, *Vitis vinifera*; Growth factors like EGF transforming growth factor β, vascular endothelial growth factor; inflammatory cytokines, protein linase, etc. were acted upon by *C. longa* (Garodia et al. 2007).

8.4 Dietary Polyphenols as Anti-cancer Agents

Reactive oxygen (ROS) and nitrogen species are produced during metabolism, and activities of the immune system and mitochondria. These are kept under check by detoxification mechanisms (Hansen et al. 2006). Polyphenols have antioxidant as well as specific biological activity against different types of cancer. These include phenolics like catechin, procyanidins (B1 & B2), phloridzin, etc. from apples and apple juices shown to exert anti-cancer activity against cell lines HT-29 (colon) and MKN45 (stomach); phloretin, quercetin, etc. against Caco-2 (colon); ellagic acid, quercetin derivatives, kaemferol 3- glucoside, cyanidin 3-glucoside, pelargonidin 3- glucoside, etc. from black berry against HL-60 (leukemia) and A549 (lung); tannic acid from black sesame against HT 29 (colon), and other phenolic derivatives active against a wide range of cell lines. Extracts of bean, cocoa, coffee, grape seeds, onion, honey, olive oil, and potato also show anti-proliferative activity against several cell lines (Roleira et al. 2015).

Massi et al. (2012) in their review stressed upon the importance of cannabidiol (CBD) in modulating the stages of tumourigenesis in several types of cancer and the need to look into CBD/CBD analogues as alternative therapeutic agents. Manju Sharma et al. (2014) described the use of non-tetrahydrocannabinol plant cannabinoids with no psychotropic effects for the management of prostate cancer. Resveratrol (3,5,4′-trihydroxystilbene) is a phytoalexin, the active principle found in red wine and grape skins. It is found in compound formulations like *Triphala ghrita*, *Khadirarista*, *Madhusnuhi rasayana*, *Maha triphaladya ghrita*, and *Panchatikta guggulu ghrita* and indicated in the ayurvedic texts for management of cancer/tumour. Aluyen et al. (2012) found that resveratrol's chemoprotective effect is dose and duration dependent. They also report synergistic activity of resveratrol with other cancer drugs. Tsubura et al. (2011) reported the inhibitory activity of garlic and its derivatives on breast cancer cell lines and the increased efficiency of oil-soluble fraction containing diallyl disulfide . Curcumin and resveratrol showed a synergistic cancer effect on colon/colorectal cancer (Majumdar et al. 2009; Patel et al. 2010). Du et al. (2013) suggested the combination treatment of these to be a promising novel anti-cancer strategy against liver cancer. Mangal et al. (2013) have developed a database, Naturally Occurring Plant-based Anti-cancer Compound-Activity-Target (NPACT, http://crdd.osdd.net/raghava/npact/), with 1574 compounds that provides information on plant-based anti-cancer compounds, accessed by key word search and other advanced options. Vetrivel et al. (2009) developed another database for compounds from Indian Plants (InPACdb), providing details on the type and target of the cancer, 3D image, etc. for each compound. Greenwell and Rahman (2015) gave an insight into the use of medicinal plant compound formulations like *Triphala ghrita*, *Khadirarista*, *Madhusnuhi rasayana*, *Maha triphaladya ghrita*, and *Panchatikta guggulu ghrita*.

Alvaradoin E, and its 10 (R) isomer, alvaradoin F isolated from the leaves of *Alvaradoa haitiensis* Urb. (Picramniaceae) was found to be toxic to the KB cell line by Phifer et al. *(*2007). Alvaradoins E and F also showed inhibition of KB, LNCaP, and Col2 cells when administered intraperitonially (Mi et al. 2005).

Quassinoids found in Simaroubaceae members and a novel one 2′-(R)-O-acetylglaucarubinone isolated from *Odyendyea gabonensis* showed potent cytotoxicity against human cancer cell lines like prostate (DU145), lung (A549), and oral epidermoid carcinoma (KB) cells (Usami et al. 2010). Tanshinone I, tanshinone IIA, and cryptotanshinone exhibited significant in vitro cytotoxicity against cell lines of breast cancer, cervical cancer, etc.

In the early 1960s, the anti-cancer property of camptothecin (from *Camptotheca acuminata)*, a drug-inhibiting DNA topoisomerase1, was discovered and this revolutionized the field of chemotherapy (Wall et al. 1966; Wall 1998), also inhibiting colon and pancreatic cancer cells (Redinbo et al. 1998; Staker et al. 2002) and cancer types like breast, liver, prostate, etc.

Combretastatins are anti-cancer agents isolated from the bark of the South African tree *Combretum caffrum* (Pettit et al. 1987). Combretastatin A-4, a simple Stilbene, was found to inhibit the polymerization of brain tubulin by binding to the colchicine site (Hamel and Lin 1983). It is also cytotoxic to human cancer cell lines like MDR. CA-4 could serve as a lead molecule for drug development against cancer (McGowan and Fox 1990; El-Zayat et al. 1993). CA-4 induces apoptosis and mitotic catastrophe there by eradicating bladder cancer (Shen et al. 2010). Considering the potent activity of CA-4 for the treatment of tumours, many synthetic analogues of CA-4 have been synthesized to improve upon its cytotoxic activity and inhibition of tubulin polymerization (Ohsumi et al. 1998, Nam 2003; Tron et al. 2006). Combretastatin A4 phosphate (CA4P; fosbretabulin), a tubulin-binding vascular disrupting agent, displays potent and selective toxicity towards tumour vasculature (Tozer et al. 1999). Shen et al. (2010) described the scope for using CA-4 for intravesical therapy, as it inhibited cell migration in vitro.

Ayurveda, the traditional Indian system of medicine, is a potential treasure chest for chemicals useful in the prevention and treatment of cancer (Devi 1996). *Cedrus deodara, Berberis aristata, Picrorhiza kurroa*, and *Piper longum* L. were shown to have anti-cancer activity against cell lines (Gaidhani et al. 2013). The anti-cancer value of *Withania somnifera* (ashwagandha) documented over four decades ago is attributed to withaferin A, a crystalline steroidal compound isolated from its leaves (Shohat et al. 1976). *W. somnifera* contains steroidal lactones collectively referred to as withanolides isolated from the root or leaf (Jayaprakasam et al. 2003; Ichikawa et al. 2006). Withaferin A is found to be the most effective among these, proved by in vivo pre-clinical studies on rodent systems. It is clear that Withaferin A targets multiple molecules/pathways that may be cell line-specific (Vyas and Singh 2014). Recent studies indicate Withaferin A to be a possible chemotherapeutic drug candidate for human oral cancer (Yang et al. 2015).

Tanshinones, isolated from *Salvia miltiorrhiza*, showed significant in vitro cytotoxicity against several human carcinoma cell lines such as breast cancer cells, cervical cancer cells, prostate cancer growth, etc. (Zhang et al. 2012).

Couroupita guianensis, commonly known as Nagalinga pushpam in Tamil, was found to have anti-cancer activity against cancer cell lines, viz., Caco2, MCF-7, A-431, and HeLa, using MTT assay. In vitro, antioxidant activities against free

radicals, viz., 2,2-diphenyl-1–picrylhydrazyl (DPPH)-radical, Nitric oxide, Hydroxyl radical, etc., were also found (Ramalakshmi et al. 2014).

Plant-derived sesquiterpene lactones salograviolide A (Sal A) and iso-seco-tanapartholide (TNP) showed synergistic anti-cancer activities as reported by Mohamed Salla et al. (2013). They found increased activity when these were used together than alone. Sal A or TNP at low doses when used individually did not have an effect on cell viability, but in combination at the same concentrations they initiated apoptosis. Apotopsis caused by the combined treatment is due to the production of ROS, which induces apoptosis. The mitogen-activated protein kinase (MAPK) pathway plays a vital role in signalling apoptotis, which in turn is triggered by toxic stimuli or stress (Benhar et al. 2002, Zhang et al. 2005). Three known MAPKs, the extracellular signal-regulated kinase (ERK1/2), the c-Jun N-terminal kinase/stress-activated protein kinase, and p38, when activated induce cell death (Zhang et al. 2005). ROS accumulation also causes JNK and p38 activation, in turn leading to cell death (Guyton et al. 1996; Cho et al. 2005; Kamata et al. 2005).

Anti-cancer property has been reported for *Polygala* sp. by Alagammal et al. (2013), *Nigella sativa* by Soumya et al. (2011), and *Bauhinia variegata by* Amita Mishra et al. (2013).

Garlic contains quite a few biomolecules that have antioxidant and anti-carcinogenic properties. Some of them are flavonoids like quercetin and cyaniding, ajoene, a sulphur-containing compound inhibiting mutagenesis, selenium, which is an anti-oxidant, and diallyl sulphides, all contributing anti-carcinogenic properties to it (Sakarkar and Deshmukh 2011).

Actinidia chinensis root is used against cancer in Chinese medicine. (*The wealth of India: A Dictionary of Indian Raw Materials and Industrial Products Vol –I (A-B)*1985, pp. 29.) Aloe-emodin in *Aloe vera* fights cancer and inhibits metastasis by activating macrophages and immune cells (Pecere et al. 2000). *Camellia sinensis* (tea) contains polyphenolics (catechins and gallates) with anti-mutagenic and anti-cancer activity, which gives protection against cancers of liver, oesophagus, stomach, intestine, and lung (Kim et al. 1995; Dreosti 1996).

Ginkgolide-B *from Ginkgo biloba* prevents cancer proliferation by controlling the activity of the platelet-activating factor and also protects DNA from damage induced by nuclear radiation (Kleijnen and Knipschild 1992a; Tyler 1994).

Soya bean is found to induce differentiation in cancer cells by converting them to normal cells, by virtue of isoflavones. Genisten, an isoflavone found in soy, induces apoptosis in cancerous cells. It also prevents the spread of cancer by preventing platelet aggregation in turn by inhibiting the tyrosine kinase inhibitor enzyme, and also by blocking angiogenesis (Kleijnen and Knipschild 1992b).

The glycoside glycyrrhizinin in liquorice shows anti-cancer activity in animal systems (Ambasta 2000a). Gossypol from *Gossypium barbadense* has shown selective toxicity towards cancerous cells (Ambasta 2000b). Plant lignans in flax seed when converted to lignans enterolactone and enterodiol (mammalian lignans) by bacterial fermentation in the colon are anti-carcinogenic. These are structurally similar to estrogens and can bind to estrogen receptors there by inhibiting the growth of estrogen-stimulated breast cancer (Serraino and Thompson 1991, 1992).

Anti-carcinogenic activity is also shown by monoterpene compounds in *Mentha piperita* oil (Dorman et al. 2003, Romero-Jimenez et al. 2005). *Zingiber officinalis* (ginger) rhizomes contain gingerols with pronounced anti-inflammatory activity against various cancers (Katiyar et al. 1996, Kikuzaki and Nakatani 1993).

Gaidhani et al. (2013) evaluated *Taxus baccata* L and compound formulations like *Triphala ghrita*, *Khadirarista*, *Madhusnuhi rasayana*, *Maha triphaladya ghrita*, and *Panchatikta guggulu ghrita* indicated in ayurvedic texts for management of cancer/tumour. *Cedrus deodara* (Roxb.) ex Lamb. and *Berberis aristata* (Roxb.) ex DC. showed maximum anti-cancer activity (against 3 cell lines) as compared to *Withania somnifera* Dunal. (against two cell lines) and *Picrorhiza kurroa* and *Piper longum* L. (against one cell line).

8.5 Conclusions

The chapter gives a new perspective on cancer prevention and cure using biomolecules from plants/ayurvedic sources. Natural compounds tend to have an undeniable role in cancer prevention and cure. Drug discovery from medicinal plants is time consuming and cumbersome. Techniques such as nuclear magnetic resonance spectroscopy and mass spectroscopy could facilitate compound isolation from medicinal plants. Though it is challenging, medicinal plants still remain a major source/reservoir of novel drug candidates for cancer. In the near future, plant-derived compounds could hold a major share in the array of cancer medicines available for therapy.

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