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Herbal Plants Role in Prevention and Management of Various Cancers in Community

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A B S T R A C T

Globally cancer is a disease which severely effects the human population. There is a constant demand for new therapies to treat and prevent this life-threatening disease. Scientific and research interest is drawing its attention towards naturally-derived compounds as they are considered to have less toxic side effects compared to current treatments such as chemotherapy. The Plant Kingdom produces naturally occurring secondary metabolites which are being investigated for their anticancer activities leading to the development of new clinical drugs. Cancer has been a constant battle globally with a lot of development in cures and preventative therapies. The disease is characterized by cells in the human body continually multiplying with the inability to be controlled or stopped. Consequently, forming tumours of malignant cells with the potential to be metastatic. Current treatments include chemotherapy, radiotherapy and chemically derived drugs. Treatments such as chemotherapy can put patients under a lot of strain and further damage their health. Therefore, there is a focus on using alternative treatments and therapies against cancer. For many years herbal medicines have been used and are still used in developing countries as the primary source of medical treatment. Plants have been used in medicine for their natural antiseptic properties. Thus, research has developed into investigating the potential properties and uses of terrestrial plants extracts for the preparation of potential nanomaterial based drugs for diseases including cancer. Many plant species are already being used to treat or prevent development of cancer. Multiple researchers have identified species of plants that have demonstrated anticancer properties with a lot of focus on those that have been used in herbal medicine in developing countries to treat cancer.

Keywords: Cancer, Health, Medicine, Medicinal plants, diseases, clinical drugs.

A R T I C L E I N F O

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1. Introduction

Cancer remains one of the leading causes of morbidity and mortality globally. Amongst the non-communicable diseases, cancer is the second leading cause of death, after cardiovascular disease. Cancer is responsible for one in eight deaths worldwide more than AIDS, tuberculosis, and malaria together. Overall cancer incidence and mortality are higher in North America, Australia, New Zealand and Western Europe compared to the rest of the world]. In the United States, one in four deaths is attributed to cancer. Globally, the number of cancer deaths is projected to increase from 7.1 million in 2002 to 11.5 million in 2030. Chemotherapy is routinely used for cancer treatment. Since cancer cells lose many of the regulatory functions present in normal cells, they continue to divide when normal cells do not. This feature makes cancer cells susceptible to chemotherapeutic drugs. Approximately five decades of

systemic drug discovery and development have resulted in the establishment of a large collection of useful chemotherapeutic agents. However, chemotherapeutic treatments are not devoid of their own intrinsic problems. Various kinds of toxicities may occur as a result of chemotherapeutic treatments. For example, 5-fluorouracil, a common chemotherapeutic agent, is known to cause myelotoxicity, cardiotoxicity and has even been shown to act as a vasospastic agent in rare but documented cases. Another widely used chemodrug, doxorubicin causes cardiac toxicity, renal toxicity, and myelotoxicity. Similarly, bleomycin a well-known chemotherapeutic agent is known for its pulmonary toxicity. In addition, bleomycin shows cutaneous toxicity. Cyclophosphamide, a drug to treat many malignant conditions, has been shown to have bladder toxicity in the form of hemorrhagic cystitis, immunosuppression, alopecia at high doses cardiotoxicity[6].

Natural plants have been used to prevent and to treat various diseases for thousands of years. The ancient Chinese emperor, the Red Emperor, or *Shen Nung*, compiled the medicinal herbal literature**,** *Pentsao* in 2,800 BC. In dealing with diseases, prevention is considered a superior approach. As illustrated by the *Huang-Di Nei-Jing*, a manuscript believed being written by the ancient Chinese emperor, the Yellow Emperor, "The Saint treats those ill-to-be rather than those being ill, and **cares for** those in **normality** rather than those in chaoses. Drug a disease after it's developed, or quench a chaos after it's evident, is same as dig a well when in thirsty, or casting a sword in a battle Is that somewhat late.

There are excellent **sources** of bioactive components exerting their health beneficial effects, and very often, **these sources** are materials for gourmet food consumptions. Certain bioactive components from the plants have been confirmed for their anti-cancer activities. There is an estimate that approximately 50-60% of cancer patients in the United States utilize agents derived from different parts of plants or nutrients (complementary and alternative medicine), exclusively or concomitantly with traditional therapeutic regimen such as chemotherapy and/or radiation therapy. These include curcumin from tumeric, genistein from soybean, tea polyphenols from green tea, resveratrol from grapes, sulforaphane from broccoli, isothiocyanates from cruciferous vegetables, silymarin from milk thistle, diallyl sulfide from garlic, lycopene from tomato, rosmarinic acid from rosemary, apigenin from parsley, and gingerol from gingers, just to name a few.

2. Biopharmaceutics considerations

Bioavailability is another challenge needs to be overcome for many phytochemicals. Another example of curcumin is that it shows low bioavailability in earlier studies. To improve that, nanotechnology, liposomes, micelles, various coating materials, and phospholipid complexes have been applied to increase its water solubility and to enhance its bioavailability. Genistein has limited bioavailability in earlier studies. Cohen *et al* studied the effect of complexation of genistein with high-amylose corn starch and achieved twice as high in genistein concentration in the plasma versus controls.

Phytochemicals' crystal structures, polymorphism, amorphism, appropriate salt selection, excipient comparability, etc. should be considered so as to develop a robust phytochemical drug. The physical forms of a phytochemical may impact the solubility in various physiological conditions, absorption, variation in pharmacokinetic performance, product content consistency in large scale manufacturing, drug stability, degradation product formation and pathway during product storage. Class summarized the importance and quantification approaches in characterizing the crystal form of the drug substance during drug development.

Most drug products or nutrition supplements in oral dosage forms are tested *in vitro* using United States Pharmacopeia (USP) Apparatus I or II to analyze the percent dissolved values of the drug active ingredients in selected biorelevant dissolution media at a few sampling time points. The dissolution test not only evaluates their potential bioavailability *in vivo*, but also serves as a means to monitor the quality of the drug product after it is manufactured. It is possible to establish a dissolution *in vitro in vivo* correlation by applying relevant mathematical algorism with software such as WinNonlin® or GastroPlus™. Soh, Heng updated the *in vitro* dissolution techniques of pharmaceutical solids recently.

Bioavailability of orally dosed phytochemicals

Phytochemicals are naturally originated and many are components of daily foods. Therefore, though not exclusively, studies have been emphasized on oral administration for the phytochemicals. Dosing via oral route may show low bioavailability due to excessive metabolism by Phase I and Phase II drug metabolism enzymes (DME). This may hamper the phytochemicals from being available for absorption and distribution in the body. Phase I drug metabolism enzymes include mostly cytochrome P450 and can be found in most tissues of the body. They are invovlved in oxidation, reduction, or hydrolysis to increase the polarity of a drug. An important aspect of phytochemicals is their ability to impact CYP enzymes. Famous examples include grafefruit juice inhibit CYP3A4 mediated metabolism of certain drugs and cause the increased bioavailability of the drug and potential toxicity. Other phytochemical related examples include watercress inhibites CYP2E1 which may complicate the absorption of some drugs. Phase II drug metabolizing enzymes include conjugating enzymes for glucuronidation, sulfation to increase the water solubility and excretability of a drug. Excessive metabolism by Phase II DMEs may also relate to a drug's poor bioavailability. Recent book chapter by Tompkins *et al* on liver drug metabolism and bioavailability had an excellent discussion on this topic.

Toxicity considerations

Although phytochemicals are extracted from natural plants and are generally considered non-toxic, they can exert their toxicities to the animal or human systems at certain situation (drug-drug interaction) and concentration, which impede their application in the clinical studies and further

application in chemoprevention and treatment. This involves another major challenge: the controversy of the effects of the natural compounds. This controversy may be due to synergistic effects existing in natural compounds when consumed as a whole rather than a single extracted compound. Lambert *et al* analyzed benefits *vs* risks on possible controversy over dietary polyphenols. Some of the antioxidant activities of the natural compounds demonstrated *in vitro* studies are not reproducible *in vivo*. Even in some occasions, natural phytochemicals demonstrate hepatic and gastrointestinal toxicities, e.g., by green tea polyphenols (EGCG) at high doses. Therefore, a thorough understanding of the compounds and their pharmacological effects are essential for natural phytochemicals' drugability and their transition from bench top to patients' bedside.

Regulatory considerations

An unavoidable question on phytochemical drugability is regulatory considerations. Thus far, many phytochemicals are sold as dietary supplements in the market, which are governed by relatively liberal regulations of the health authority (i.e., FDA) compared to those of prescription drugs. FDA defines drug as: articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease and articles (other than food) intended to affect the structure or any function of the body of man or other animals. (FD&C Act section 201(g)(1).

Medicinal plants and cancer

The anticancer properties of plants have been recognized for centuries. Isolation of podophyllotoxin and several other compounds (known as lignans) from the common mayapple (Podophyllum peltatum) ultimately led to the development of drugs used to treat testicular and small cell lung cancer. The National Cancer Institute (NCI) has screened approximately 35,000 plant species for potential anticancer activities. Among them, about 3,000 plant species have demonstrated reproducible anticancer activity.

Many studies have focused on the chemoprotective properties of plants such as anticarcinogenic properties of Abrus precatorius on Yoshida sarcoma in rats, fibrosarcoma in mice and ascites tumor cells. Similarly, Dhar et al. have examined the anticancer properties of Albizzia lebbeck on sarcoma in mice and Alstonia scholaries on benzo[a]pyrene-induced forestomach carcinoma in humans. Other plants that have shown anticarcinogenic properties include Anacardium occidentale in hepatoma, Asparagus racemosa in human epidermoid carcinoma, Boswellia serrata in human epidermal carcinoma of the nasopharynx, Erthyrina suberosa in sarcoma, Euphorbia hirta in Freund virus leukemia, Gynandropis pentaphylla in hepatoma, Nigella sativa in Lewis lung carcinoma, Peaderia foetida in human epidermoid carcinoma of the nasopharynx, Picrorrhiza kurroa in hepatic cancers, and Withania somnifera in various tumors.

The anticancer characteristics of a number of plants are still being actively researched and some have shown promising results. Some plants and plant products that have shown promise as anticancer agents are discussed in detail in the following sections[7-15].

Tinospora cordifolia (Wild) Miers

Tinospora cordifolia, also known as guduchi in Sanskrit, giloya in Hindi and heartleaf moonseed plant in English, is a bulky, smooth, climbing deciduous shrub lacking bristles. The most commonly used part of the shrub is the stem, but roots are also known to contain important alkaloids. This shrub is commonly found in India, Myanmar, Sri Lanka and China.

According to ancient Ayurvedic lexicons, T. cordifolia is also referred to as "amrita". The term "amrita" is ascribed to this plant due to its ability to impart youthfulness, vitality and longevity. The stem of T. cordifolia is used for general debility, dyspepsia, fever, urinary disease, and jaundice. The extract of its stem is used in treating skin diseases. There are certain curative properties of the root of T. cordifolia which allow for its use as antidote in snake bite, in combination with other drugs. T. cordifolia is well known in modern medicine for its adaptogenic, immunomodulatory, anti-oxidant activities. T. cordifolia is also known to have anti-inflammatory, anti-arthritic, anti-allergic properties. This plant is also useful in treating skin diseases, vomiting, anemia, piles, chronic fever, and emaciation. The methanol extract of Tinospora contains phenylpropanoids, norditerpene furan glycosides, diterpene furan glycosides and phytoecdysones. The roots of T. cordifolia are also reported to contain other alkaloids like choline, tinosporin, columbin, isocolumbin, palmatine, tetrahydropalmatine and magnoflorine.

T. cordifolia effectively kills HeLa cells in vitro, suggesting its potential as an anticancer agent. A dose-dependent increase in cell death was observed in HeLa cells treated with T. cordifolia extract as compared to the controls. The anticancer activity of dichloromethane extract of T. cordifolia in the mice transplanted with Ehrlich ascites carcinoma has been demonstrated. T. cordifolia extract showed a dose-dependent increase in tumor-free survival with highest number of survivors observed at 50 mg/kg dose.

Ziziphus nummularia Wight

Ziziphus nummularia, also known as bhukamtaka sukhsharanphala in Sanskrit, harbor in Hindi and wild jujube in English, is a thorny small bush or a divaricating shrub, with pale-purplish stems and or grey-velvety stipular prickles in pairs. The different parts of the plant that are used for medicinal purposes are root, bark, stem, flowers and seeds. This shrub is generally found in India, Pakistan, Afghanistan, Egypt, Iran, Iraq, and Israel.

Betulin and betulinic acid (chemical structures shown on next page) are present within the bark and stem of Z. nummularia and have been shown to have antitumor activity. Betulinic acid glycosides produce differential cytotoxicity, such that cancer cell lines are more sensitive than normal cells. Similarly, betulinic acid, a naturally occurring pentacyclic triterpenoid, shows selective cytotoxicity against a variety of tumor cell lines. Betulinic acid has been suggested to induce apoptosis by generation

of reactive oxygen species, inhibition of topoisomerase I, activation of the mitogen activated protein kinase (MAP kinase) cascade, inhibition of angiogenesis, and modulation of pro-growth transcriptional activators and aminopeptidase-N activity. Furthermore, betulinic acid has been shown to induce apoptosis by a p53- and CD95-independent mechanism. These mechanisms may be responsible for the ability of betulinic acid to effectively kill cancer cells that are resistant to other chemotherapeutic agents.

It has been shown that combined treatment of betulinic acid and anticancer drugs, act in concert, to induce loss of mitochondrial membrane potential and the release of cytochrome c and second mitochondria derived activator of caspase (Smac) from mitochondria. These changes are suggested to result in the activation of caspases and induce apoptosis. Notably, betulinic acid augments the anticarcinogenic effect of different cytotoxic compounds of different modes of action (for example, doxorubicin, cisplatin, taxol, or actinomycin D). Importantly, betulinic acid potentiates the apoptotic effect of anticancer drugs in different tumor cell lines, including p53 mutant cells, as well as primary tumor cells, but not in human fibroblasts indicating some tumor specificity.

Andrographis paniculata (Burm. F.) Nees

Andrographis paniculata, commonly known as bhunimba and kalmegha in Sanskrit, kiryat in Hindi and the king of bitters and chiretta in English, is found in India and Sri Lanka. The parts of the plant generally used for medicinal purposes are the roots and the leaves. A. paniculata extract contains diterpenes, flavonoids and stigmasterols. The primary medicinal component of Andrographis is the diterpene andrographolide (chemical structure shown below). Andrographolide, described as a "diterpene lactone" due to its ring like structure, has a very bitter taste and has a colorless crystalline appearance. Andrographis leaves contain the highest concentration of andrographolide (~ 2.25%), while the seeds contain the lowest.

A. paniculata is used in the treatment of wide variety of conditions such as jaundice, cholestasis and as an antidote for heptotoxins. Its anti-HIV activity has also been reported. Studies conducted on mice have shown that A. paniculata is a potent stimulator of the immune system and that it activates both the antigen-specific and non-specific immune responses. Due to its ability to activate both types of immune response, A. paniculata is a potent chemoprotective agent and is effective against a variety of infectious and oncogenic agents. Andrographolide shows cytotoxic activity against a variety of cancer cells. For example, andrographolide exerts cytotoxic effects against KB human epidermoid cancer cells, P388 lymphocytic leukemia cells, MCF-7 breast cancer cells and HCT-116 colon cancer cells. Further, andrographolide causes growth inhibition in the colon cancer cell line HT 29, enhances the growth and division of human peripheral blood lymphocytes and exerts pro-differentiative effects on the mouse myeloid leukemia M1 cell line.

Alcoholic extract of A. paniculata has been shown to cause a significant increase in the activities of glutathione-S-transferase (GST), DT-diaphorase (DTD), superoxide dismutase (SOD) and catalase, differentially in the lung, liver, kidney and forestomach. It also causes a decrease in the activity of lacate dehydrogenase (LDH) and malondialdehyde (MDA). Andrographis also results in alterations in the level of glutathione (GSH) [56], and GSH significantly contributes to its function of detoxifying the xenobiotics which may play a causative role in the carcinogenic process. A major chemical constituent of A. paniculata, andrographolide has also shown significant anticancer and immuno-stimulatory activities. The in vivo results conducted in immuno-competent Swiss albino mice, demonstrated that andrographolide significantly inhibits the cancer cell proliferation without showing any signs of toxicity in mice, even at relatively high doses[16-25].

Centella asiatica Linn

Centella asiatica, known as mandukaparni in Sanskrit, brahmamanduki in Hindi and asiatic pennywort in English, is another plant that has shown potential as an anticancer agent. This plant is commonly found in India, Australia, Pacific Islands, New Guinea, Malaysia, and Iran. The whole plant or its leaves are being traditionally used for their therapeutic properties. Partially purified fractions of C. asiatica, dose-dependently inhibited the proliferation of transformed cell lines, including Ehrlich ascites tumor cells and Dalton's lymphoma ascites tumor cells. However, practically no toxic effects were detected in normal human lymphocytes. Partially purified fractions of C. asiatica also significantly suppressed the proliferation of mouse lung fibroblast cells in long-term culture. Oral administration of C. asiatica extracts slowed the development of solid and ascites tumors and increased the total life span of tumor-bearing mice

Curcuma longa Linn

Curcuma longa is popularly known as turmeric in English, haridra in Sanskrit and haldi in Hindi. The rhizome of the plant is traditionally used in cooking. The active ingredient of this plant is curcumin (diferuloylmethane, chemical structure shown below), a polyphenol derived from the rhizome of the plant. Turmeric is used for both cancer prevention and treatment. The anticancer potential of curcumin is associated with its ability to inhibit proliferation in a wide variety of tumor cell types. The anti-proliferative properties of curcumin may be related to its ability to down-regulate the expression of a number of genes, including NF-kappa B, Activator Protein 1 (AP-1), Epidermal growth receptor 1 (EGR-1), cycloxygenase 2 (COX2), lysyl oxidase (LOX), nitric oxide synthase (NOS), matrix metallopeptidase 9 (MMP-9), and tumor necrosis factor (TNF). Moreover, turmeric reduces the expression of various chemokines, cell surface adhesion molecules, cyclins and growth factor receptors, including epidermal growth factor receptor (EGFR), and human epidermal growth factor receptor 2 (HER2). In addition to its effects on gene expression, turmeric inhibits the activity of c-Jun N-terminal kinase, protein tyrosine kinases and protein serine/threonine kinases. Turmeric has also been shown to inhibit tumor cell invasion and metastasis in vitro by

reducing MMP-2 activity and by inhibiting HEp2 (epidermoid carcinoma cell line) cell invasion.

Curcumin and its derivatives demonstrated significant inhibition of VEGF and bFGF-mediated corneal neovascularization and directly inhibited angiogenesis in vivo and in vitro. In addition to its antitumor effects in vitro, curcumin has been shown to prevent colon and gastric cancers in rodents. The mechanism underlying the protective effect of curcumin is suggested to be related to its ability to inhibit the growth of several tumor-associated and angiogenesis-associated genes.

Phyllanthus amarus Schumach. & Thonn

Phyllanthus amarus is found in tropical Asia, especially in warmer parts of India and is known as bhumyamalaki in Sanskrit, jaramla in Hindi and stone breaker in English. The whole plant, leaves, roots and shoots are reportedly used for their medicinal values. P. amarus contains various lignans, flavanoids and tannins, and evidence suggests that P. amarus extract may exert antitumor effects. Oral administration of P. amarus extract significantly increased the life span and reduced tumor size in mice bearing Dalton's lymphoma ascites (DLA) and Erlich ascites carcinoma (EAC).

P. amarus plant extract has been reported to result in a significant decrease in n-nitrosodiethylamine (NDEA)-induced tumor incidence. Additionally, a decrease in tumor marker enzymes and liver injury markers has been reported. P. amarus extract has been shown to inhibit DNA polymerase of hepatitis B virus and related hepatitis viruses and down regulates hepatitis B virus mRNA transcription and translation. The extract of P. amarus has been shown to inhibit aniline hydroxylase, a P-450 enzyme responsible for the activation of carcinogens. The extract of P. amarus inhibited the activity of cdc 25 tyrosine phosphatase, which is a key enzyme involved in cell cycle regulation. The extract of P. amarus resulted in the inhibition of the activity of topoisomerase I and II in Sacchromyces cerviacae mutant cell cultures. P. amarus extract has also been reported to have anti-angiogenic effects in mice bearing Lewis lung carcinoma with evidence to interfere with the migration of vascular endothelial cells. The lignan-rich fraction of the hexane extract of P. amarus, and the various purified lignans namely nirtetralin (NIRT), niranthrin (NIRA), phyllanthin (PHYLLA), phyltetralin (PHYLT) (chemical structures shown below) have been reported to be effective in inhibiting P-gp (P-glycoprotein) function in vitro.

Annona atemoya Mabb./ Annona muricata Linn

Annona atemoya/muricata is a native of Caribbean, Central and South America. It is also commonly grown in South East Asia especially in eastern part of India. This plant is traditionally known as mamaphal in Hindi and sour-sop of America in English. The parts of the plant that are generally used for medicinal purposes are the root, bark, leaf and fruit. The fruit of A. atemoya contains bullatacin (chemical structure shown below), an acetogenin known to have antitumor properties. Bullatacin induces chromatin margination and tumor cell condensation, followed by apoptosis. A. atemoya contains two annomuricins namely A and B, which have shown cytotoxicity in human solid tumor cell lines A-549 lung carcinoma, MCF-7 breast carcinoma, and HT-29 colon adenocarcinoma cell line. A. atemoya contains several other acetogenins that have also been shown to selectively induce cell death in tumor cells in vitro.

Mappia foetida Miers. / Nothapodytes foetida Miers

Mappia foetida/ Nothapodytes foetida is generally found in tropical countries. The medicinal properties of M. foetida have recently gained international attention. The active component of M. foetida tree wood is camptothecin (chemical structure shown below), a potent chemotherapy drug used to treat leukemia. Recent studies have indicated that an endophytic fungus which grows on this plant also produces the camptothecine. Camptothecines have broad spectrum of antitumor activities both in vitro and in vivo. For example, camptothecines have been shown to be effective inhibitors of nucleic acid synthesis in HeLa cells and L-120 cells. The anti-neoplastic activity of camptothecine has been attributed to its inhibitory action on the nuclear enzyme type-1 DNA topoisomerase (topo-1). This alkaloid as well as several semisynthetic or fully synthetic analogues, are in various stages of preclinical and clinical trials.

***Withania somnifera* (Linn.) Dunal**

Withania somnifera (Linn.) Dunal (Solanaceae) known as ashwagandha in Sanskrit and Hindi, winter cherry in English, is a small subtropical shrub. The roots and leaves of *W. somnifera* have been used in the Indian traditional system of medicine Ayurveda, and the plant is marketed world-wide because of its medicinal properties. It is also one of the members of GRAS (generally regarded as safe) category of plants that has found several therapeutic uses.

W. somnifera has been in use in the Indian traditional system of medicine for ages for its energy-promoting and anti-stress benefits. It has been recently reported that Th1-immune up-regulation is a major effect of the root constituent withanolide A. Withaferin A, another chemical constituent of *W. somnifera*, is distributed mostly in leaves and produces rapid apoptosis in cancer cells. However, synthesis of these withanolides or their isolation from plants in therapeutic amounts has posed serious limitations for their effective utility in clinics. Scientists at Indian Institute of Integrative Medicine, Jammu, India, have devised a formulation, which offers a unique novelty where the root and leaf extracts of an elite variety of *W. somnifera* are mixed in a certain ratio to obtain a defined pharmaceutical composition rich in withanolide A and withaferin A [Indian Patent: 0202NF2006; Del 01321 dated 19-06-2007]. This *W. somnifera* formulation appears to offer a multi-modal action against cancer disease as evidenced by their current studies.

***Cedrus deodara* (Roxb. Ex. D. Don) G. Don**

Cedrus deodara (deodar cedar, himalayan cedar, or deodar in Hindi, devdar in Sanskrit, xue song in Chinese) is native to the western Himalaya (Hind Kush mountains), eastern Afghanistan, northern Pakistan, northwest and northcentral India, southwestern Tibet and western Nepal. It is widely grown as an ornamental tree and planted in parks and large

gardens for its drooping foliage. The name "deodar" is derived from modern Indian language derivatives of the Sanskrit name "devdar", meaning "timber of the gods".

***Oswellia serrata* Roxb**

Boswellia serrata is a deciduous middle sized tree, which is most commonly found in tropical parts of Asia and Africa. The gum from the plant is tapped from incisions made on the trunk of the tree, which is then stored in specially made bamboo baskets and converted into different grades of material according to flavor, color, shape and size.

The step towards development of cancer involves alterations of epigenetic processes and their deregulation. The control of hypermethylation of tumour-suppressor genes on CpG islands is deregulated in cancer cells. This can result in gene silencing and inactivation of tumour-suppressor genes . Drugs which can inhibit or reverse epigenetic alterations have been in development over recent years.

Chemically derived epigenetic drugs have been developed and undergone trials such as 5-azacytidine (azacitidine; Vidaza) and 5-aza-2'-deoxycytidine (decitbine; Dacogen) which are both DNMTi and HDACi such as suberoyanilde hydroxamic acid (SAHA, Vorinostat, Zolinza) and FK228 (Romidespin, Istodax). However, it is difficult to engineer a chemically derived drug which is non-toxic to normal cells and is specific to cytotoxicity of cancer cells. Therefore, development and research into naturally derived compounds to be used for anticancer treatment is becoming high in demand with a focus on those derived from plant species and their natural products.

There are many forms of cancer amongst the human population but they share similar characteristics or genotypes such as insensitivity to signals which inhibit cell growth making their replication limitless. Apoptosis is evaded and never induced in cancer cells and angiogenesis is sustained within the tumour tissue allowing survival of cancer cells. Plant derived compounds have demonstrated properties to inhibit cancer cell activity such as inhibiting proliferation of cancer cells and inducing apoptotic cell death[26-30].

3. Compounds with anticancer properties

Medicinal plants have been used for thousands of years in folk medicines in Asian and African populations and many plants are consumed for their health benefits in developed nations. According to the World Health Organisation (WHO) some nations still reply of plant-based treatment as their main source of medicine and developing nations are utilising the benefits of naturally sourced compounds for therapeutic purposes. Compounds which have been identified and extracted from terrestrial plants for their anticancer properties include polyphenols, brassinosteroids and taxols.

Polyphenols

Polyphenolic compounds include flavonoids, tannins, curcumin, resveratrol and gallacatechins and are all considered to be anticancer compounds. Resveratrol can be found in foods including peanuts and grapes and red wine. Gallacatechins are present in green tea. It is thought including polyphenols in a person's diet can improve health and reduce risk of cancers by being natural antioxidants.

The cytotoxicity of polyphenols on a range of cancer cells has been demonstrated and their antioxidant properties determined. Polyphenols are thought to have apoptosis inducing properties showing anticancer properties which can be utilized. The mechanism in which polyphenols are thought to carry out apoptosis initiation is through regulating the mobilization of copper ions which are bound to chromatin inducing DNA fragmentation. In the presence of Cu(II), resveratrol was seen to be capable of DNA degradation. Other properties plant polyphenols show is their ability to interfere with proteins which are present in cancer cells and promoting their growth. Cancer agents may be altered through the polyphenol regulating acetylation, methylation or phosphorylation by direct bonding. For example, curcumin treated cancer cells in various cells lines have shown suppression of the Tumour Necrosis Factor (TNF) expression through interaction with various stimuli.

Flavonoids

Flavonoids are from the polyphenolic compounds and constitute a large family of plant secondary metabolites with 10,000 known structures. They are physiologically active agents in plants and becoming of high interest scientifically for their health benefits. Various plants have been investigated for their flavonoid content and how these compounds affect cancer cells, such as fern species and plants used in traditional Chinese medicines like the litchi leaf . There is a high content of flavonoid compounds such as anthocyanins, flavones, flavonols, chalcones and many more which can be found in just one structure of the plant like its seed. Purified flavonoids have also shown anticancer activities against other human cancers including; hepatoma (Hep-G2), cervical carcinoma (Hela) and breast cancer (MCF-7). The flavonoids extracted from *Erythrina suberosa* stem bark (4'-Methoxy licoflavanone (MLF) and Alpinumi soflavone (AIF)) were shown to have cytotoxic effects in HL-60 cells (human leukaemia). MLF and AIF induced apoptosis through intrinsic and extrinsic signalling pathways. The mitochondrial membrane potential is significantly reduced due to the induction of apoptotic proteins. With mitochondria damage to cells the cancer cells cannot survive. As previously mentioned polyphenols can inhibit or alter the regulation of proteins and other agents which may be contributing to the survival of cancer cells. Signal Transducer and Activator of Transcription (STAT) proteins are anti-apoptotic and contribute to cancer cell growth. MLF and AIF inhibit members of this family of proteins by preventing their phosphorylation needed for the cancer cells survival. Also, these flavonoids inhibit the expression of NF-κB which is needed for cancer cell survival and angiogenesis and proliferation.

Brassinosteroids

Brassinosteroids (BRs) are naturally occurring compounds found in plants which play roles in hormone signalling to regulate growth and differentiation of cells, elongation of stem and root cells and other roles such as resistance and tolerance against disease and stress. Also, BRs are used for regulation of plant senescence. They are essential for plant

growth and development. BRs are another naturally occurring compounds which have demonstrated therapeutic significance in the cause against cancer.

Two natural BRs have been used in investigations with cancerous cells to demonstrate the anticancer properties that these compounds possess. 28-homocastasterone (28-homoCS) and 24-epibrassinolide (24-epiBL) have demonstrated anticancer effects on various cancer cell lines and proven to be effective at micromolar concentrations. A characteristic of cancer cells is that they do not naturally undergo apoptosis and proliferate indefinitely. BRs can induce responses necessary for growth inhibition and induce apoptosis by interacting with the cell cycle. BRs have been used in investigations to treat a range of cancer cell lines which include; T-lymphoblastic leukaemia CEM, multiple myeloma RPMI 8226, cervical carcinoma HeLa, lung carcinoma A-549 and osteosarcoma HOS cell lines. Also included are cell lines in breast cancer and prostate cancer. Estrogen receptor (ER), epidermal growth factor receptor (EGFR) and human EGFR-2 (HER-2) are some of the critical proteins which are targeted in treatment of breast cancer as they are abundant in breast cancer cells such as MCF-7, MDA-MB-468, T47D and MDA-MB-231 In prostate cancer cells (LNCaP and DU-145 cell lines) the androgen receptor (AR) is a critical protein involved in its development and shares a similar structure to ER. BRs will interact or bind to receptors of these proteins and inhibit the growth of both hormone sensitive and hormone insensitive cancer cells. Also, BRs can induce cell cycle blockage. Treatment of breast cancer cell lines with 28-homoCS and 24-epiBL showed reduction in cyclin proteins which are involved in G_1 cell cycle phase. At this phase in the cell cycle cells will either under repair or enter apoptosis, treatment with BRs induces apoptosis at this stage which cancer cells would not be able to do naturally without treatment. In prostate cancer cell lines, LNCaP and DU-145, the balance of apoptotic proteins which promote cell survival and those which induce programmed cell death changes with BRs treatment. The levels of the Bax pro-apoptotic protein increase after BRs treatment and anti-apoptotic proteins such as Bcl-2 are reduced. Along with their anticancer properties BRs generate different responses in normal and cancer cells.

4. Conclusion

Cancer is becoming a high profile disease in developed and developing worlds. In 2007 the WHO published that in 2005, 7.6 million people died from cancer related diseases with the majority of these people living in low-income countries. Chemically-derived drugs have been developed and other cancer treatments pre-exist[31-32]. However, current methods such as chemotherapy have their limitations due to their toxic effects on non-targeted tissues furthering human health problems. Therefore, there is a demand for alternative treatments with naturally-derived anticancer agents with plants being the desired source. The secondary metabolites in the plant kingdom such as polyphenols, flavonoids and brassinosteroids have been studied for their potential use as anticancer agents. Collectively they have been shown to possess anticancer activities which include; antioxidant activity; inhibition of cancer cell growth; induction of apoptosis; target specificity; cancer cell cytotoxicity. Plant-derived drugs have been developed from positive results in research and have progressed into clinical trials. Drugs derived from vinca alkaloids were some of the first compounds to be utilized and are developing in clinical Phase III trials along with Pacitaxel and other anticancer agents. These compounds are readily available from the natural environment and are relatively non-toxic to healthy human cells. Also there are currently developments using new technologies such as nanoparticles to be used in administration of anticancer compounds and therapies. Their development could be applied to control sustained drug release and help in aims to create drugs that are tissue specific reducing severe side effects of treatments. Increasing demand for plant-derived drugs is putting pressure on high-value medicinal plants and risking their biodiversity. Increasing populations, urbanization and deforestation are contributing to species endangerment in developing countries. To aid conservation of these species germplasm conservation, cryopreservation, tissue cultures and plant part substitution strategies need to be in place.

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