MEDICINAL PLANTS AS COMBATING STRATEGY AGAINST CANCER: A REVIEW

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Abstract

Cancer is the most deadly disease that causes serious health problems, physical incapacities, mortalities, and morbidities around the globe. It is the second driving reason for death all over the world. Although great advances have been made in the treatment of cancer progression, still significant deficiencies and room for improvement remain. Chemotherapy produced a number of undesired and toxic side effects. Natural therapies, such as the use of plant-derived products in the treatment of cancer, may reduce adverse and toxic side effects. However, many plants exist that have shown very promising anticancer activities in vitro and in vivo but their active anticancer principle has yet to be evaluated. Consolidated endeavours of botanist, pharmacologist and scientific experts are required to discover new lead anticancer constituent to fight disease. This study will help researchers to assemble the information of new plant derived bioactive molecules which have been assessed for anticancer properties under in vitro and in vivo conditions.

Keywords: Cancer treatment, Medicinal Plant, Bio-active compounds

Introduction

Cancer has emerged as an important health problem in the developed and the developing countries and has become the second leading cause of death globally. It is estimated that 9.6 million deaths occur in 2018 due to this disease. Globally, about 1 in 6 deaths is due to cancer [1]. As per the reports of International Union Against Cancer (UICC), every year, more than 11 million new cases of cancer are diagnosed among them more than 7 million people die of which maximum percentage(70 %)is from low and middle-income countries.

By 2040, the global burden is expected to grow upto 27.5 million new cancer cases and 16.3 million cancer deaths may simply occur due to the growth and aging of the population. However, this burden will be considerably larger due to increasing prevalence of factors that increase risk, such as smoking, unhealthy diet, physical inactivity, and fewer pregnancies. Cancers related to these factors, such as lung, breast, and colorectal cancers, are already on the rise in economically transitioning countries, a trend that will continue if preventive measures are not widely applied.

Cancer, although a dreadful disease, is at the same time a fascinating biological phenotype. The relentless attack by cancer continues to extract a devastating price on a worldwide basis. The devastation caused by cancer is staggering to contemplate. So, the distribution of cancer in the world is very well known than any other group of disease. Although cancer is considered to be more of a developed world issue, in fact rate of all cancers was 1.8 times higher in more developed compared with less developed countries [2]. We estimate that there will be 18.1 million new cases (17.0 million excluding nonmelanoma skin cancer) and 9.6 million cancer deaths (9.5 million excluding NMSC) worldwide in 2018 (Table 1). Chemotherapy as well as conventional treatment for the cure of cancer causes the adverse and toxic side effects therefore fails to control the cancer disease. The alternate solution for the harmful effects of synthetic agents is the use of medicinal plants [3].

Table 1. New Cases and Deaths for Cancers and All Cancers Combined in 2018

CANCER SITE	NO. OF NEW CASES (% OF ALL SITES)	NO. OF DEATHS (% OF ALL SITES)
Lung	2,093,876 (11.6)	1,761,007 (18.4)
Breast	2,088,849 (11.6)	626,679 (6.6)
Prostate	1,276,106 (7.1)	358,989 (3.8)
Colon	1,096,601 (6.1)	551,269 (5.8)
Nonmelanoma of Skin	1,042,056 (5.8)	65,155 (0.7)
Stomach	1,033,701 (5.7)	782,685 (8.2)
Liver	841,080 (4.7)	781,631 (8.2)
Rectum	704,376 (3.9)	310,394 (3.2)
Oesophagus	572,034 (3.2)	508,585 (5.3)
Cervix uteri	569,847 (3.2)	311,365 (3.3)
Thyroid	567,233 (3.1)	41,071 (0.4)
Bladder	549,393 (3.0)	199,922 (2.1)
Non-Hodgkin lymphoma	509,590 (2.8)	248,724 (2.6)
Pancreas	458,918 (2.5)	432,242 (4.5)
Leukaemia	437,033 (2.4)	309,006 (3.2)
Kidney	403,262 (2.2)	175,098 (1.8)
Corpus uteri	382,069 (2.1)	89,929 (0.9)
Lip, oral cavity	354,864 (2.0)	177,384 (1.9)
Brain, nervous system	296,851 (1.6)	241,037 (2.5)
Ovary	295,414 (1.6)	184,799 (1.9)
Melanoma of skin	287,723 (1.6)	60,712 (0.6)
Gallbladder	219,420 (1.2)	165,087 (1.7)
Larynx	177,422 (1.0)	94,771 (1.0)
Multiple myeloma	159,985 (0.9)	106,105 (1.1)
Nasopharynx	129,079 (0.7)	72,987 (0.8)
Oropharynx	92,887 (0.5)	51,005 (0.5)
Hypopharynx	80,608 (0.4)	34,984 (0.4)

Hodgkin lymphoma	79,990 (0.4)	26,167 (0.3)
Testis	71,105 (0.4)	9,507 (0.1)
Salivary glands	52,799 (0.3)	22,176 (0.2)
Anus	48,541 (0.3)	19,129 (0.2)
Vulva	44,235 (0.2)	15,222 (0.2)
Kaposi sarcoma	41,799 (0.2)	19,902 (0.2)
Penis	34,475 (0.2)	15,138 (0.2%)
Mesothelioma	30,443 (0.2)	25,576 (0.3)
Vagina	17,600 (0.1)	8,062 (0.1)
All sites excluding skin	17,036,901	9,489,872
All sites	**18,078,957**	**9,555,027**

Source: GLOBOCAN 2018

Traditional Medicine –A Priceless Heritage

The plants have been used for the cure of cancer from a prolonged period of time [4]. The medicinal plants contain chemical constituents of therapeutic value [5]. These chemical substances produce physiological action on the human body. It has been shown currently by clinical studies and phytochemical investigation that many herbs exhibit anti tumor potential against various cancers [6]. In more recent history, the use of plants as medicines has involved the isolation of active compounds, beginning with the isolation of morphine from opium in the early 19th century [7]. Drug discovery from medicinal plants led to the isolation of early drugs such as cocaine, codeine, digitoxin, and quinine, in addition to morphine, of which some are still in use [8]. Moreover, drug discovery from plants involves a multidisciplinary approach combining botanical, ethno botanical, phytochemical and biological techniques. Plants continue to provide mankind the new chemical entities (lead molecules) for the development of drugs against various pharmacological targets, including cancer, HIV/AIDS, malaria, Alzheimer's disease, and pain. Although plant-based drug discovery programmes continue to provide an important source of new drug leads, numerous challenges are encountered, including procurement and authentication of plant materials, implementation of high-throughput screening bioassays and scale-up of bioactive lead compounds. More recently, drug discovery techniques have been applied to the standardization of herbal medicines, to elucidate analytical marker compounds. The potential for finding new compounds is enormous as till date only about 1% of tropical species have been studied for their pharmaceutical potential. The success of drug discovery from plants resulted in principally in the development of anti-cancer and anti-bacterial agents. The success of anti-cancer drug development can be illustrated from the efforts of the National Cancer Institute (NCI), USA.

Clinically significant cancer chemotherapeutic agents that emerged from this programme included paclitaxel (Taxus brevifolia Nutt.), hycamptamine (topotecan), CPT-11 and 9-aminocamptothecin. Furthermore, drug discovery from medicinal plants has evolved to include numerous fields of inquiry and various methods of analysis. The process typically begins with a botanist, ethnobotanist, ethnopharmacologist, or plant ecologist who collects and identifies the plant(s) of interest. The collection may involve species with known biological activity for which active compound(s) have not been isolated (e.g., traditionally used herbal remedies) or may involve taxa collected randomly for a large screening program. Phytochemists prepare extracts from the plant materials, subject these extracts to biological screening in pharmacologically relevant assays and commence the process of isolation and characterization of the active compound(s) through bioassay-guided fractionation [9].

Importance of medicinal plants in drug discovery

The biologically active compounds of higher plants have played a vital role during early development of modern medicine to combat pain and diseases. According to the organic monographs of British Pharmacopoeia of 1932, it had more than 70 percent plant-derived products. In the nineteenth and earlier centuries, natural product extracts, particularly those derived from botanical species, provided the main source of folk medicines. It is considered that because of the structural and biological diversity of their constituents, plants offer a unique and renewable source for the discovery of potential new drugs and biological entities. Drugs derived from medicinal plants can serve not only as new drugs themselves but also as drug leads suitable for optimization by medicinal and synthetic chemists. Even when new chemical structures are not found during drug discovery from medicinal plants, known compounds with new biological activity can provide important drug leads. Since the sequencing of the human genome, thousands of new molecular targets have been identified as important in various diseases [10]. With the advent of high throughput screening assays directed towards these targets, known compounds from medicinal plants may show promising and possibly selective activity. Several known compounds isolated from traditionally used medicinal plants have already been shown to act on newly validated molecular targets, as exemplified by indirubin, which selectively inhibits cyclin-dependent kinases and kamebakaurin, which has been shown to inhibit NF-kB [11-12]. The current emphasis of new drug discovery processes from plants is the development of products with new pharmacological modes of actions, apart from the known advantage of structural novelty. Exatecan, an analog of camptothecin isolated from *Camptotheca acuminata* Decne. (Nyssaceae) is being developed as an anticancer agent [13]. Vinflunine is a modification of vinblastine from *Catharanthus roseus* G. Don (Apocynaceae) for use as an anticancer agent with improved efficacy [14-15]. It is, therefore, evident that modifications of existing natural products can lead to NCEs and possible drug leads, from medicinal plants.

Anti-cancer drug discovery

Drug discovery from medicinal plants has played an important role in the treatment of cancer and, indeed, most new clinical applications of plant secondary metabolites and their derivatives over the last half century have been applied towards combating cancer [16,13]. Of all available anticancer drugs between 1940 and 2002, 40% were natural products per se or natural product derivatives with another 8% considered natural product mimics [16]. Traditionally, cancer drugs were discovered through large scale screening of plant isolates and synthetic chemicals against human cancer cell both in *in vitro* culture and animal tumor models, primarily murine leukemias. The search for anti-cancer agents from plant sources started in the 1950s with the discovery and development of the vinca alkaloids, vinblastine and vincristine, and the isolation of the cytotoxic podophyllotoxins. These discoveries prompted the United States National Cancer Institute (NCI) to initiate an extensive plant collection program in 1960, focused mainly in temperate regions. This led to the discovery of many novel chemotypes showing a range of cytotoxic activities, including the taxanes and camptothecins, but their development into clinically active agents spanned a period of some 30 years, from the early 1960s to the 1990s. This plant collection program was terminated in 1982, but with the development of new screening technologies, the NCI revived the collections of plants and other organisms in 1986. This time the focus was on the tropical and sub-tropical regions of the world, but it is interesting to note that no new plant-derived clinical anti-cancer agents have, as yet, reached the stage of general use. However, a number of agents are in preclinical development. The first agents to advance into clinical use were the so-called vinca alkaloids, vinblastine (VLB) and vincristine (VCR), isolated from the *Madagascar periwinkle*, *Catharanthus roseus* G. Don. (Apocynaceae), which was used by various ethnic cultures for the treatment of diabetes. These drugs were first discovered during an

investigation of the plant as a source of potential oral hypoglycaemic agents. Subsequently, it was found that the treatment of mice bearing transplantable lymphocytic leukaemia caused significant life extension. This led to the isolation of vinblastine and vincristine as the active agents, so their discovery may be indirectly attributed to the observation of an unrelated medicinal use of the source plant [17]. VLB in combination with other cancer chemotherapeutic drugs is used for the treatment of leukemias, lymphomas, advanced testicular cancer, breast and lung cancers, and Kaposi's sarcoma. On the other hand, VCR, in addition to the treatment of lymphomas, also shows efficacy against leukemias, particularly acute lymphocytic leukemia in childhood. More recent semi-synthetic analogues of these agents are vinorelbine (VRLB) and vindesine (VDS). These agents are primarily used in combination with other cancer chemotherapeutic drugs for the treatment of a variety of cancers. For example, VRLB has shown activity against non-small-cell lung cancer and advanced breast cancer. In addition, Podophyllotoxin was isolated from the resin of *Podophyllum peltatum* L. (Berberidaceae) but was found to be too toxic in mice, so derivatives were made with the two clinically-active agents, etoposide and teniposide, semi-synthetic derivatives of the natural product, epipodophyllotoxin (an isomer of podophyllotoxin). These derivatives are used in the treatment of lymphomas, bronchial and testicular cancers. The epipodophyllotoxins bind tubulin, causing DNA strand breaks during the G2 phase of the cell cycle by irreversibly inhibiting DNA topoisomerase II [18]. The Podophyllum species (Podophyllaceae), *P. peltatum* Linnaeus (commonly known as the American mandrake or Mayapple), and *P. emodii* Wallich from the Indian subcontinent, have a long history of medicinal use, including the treatment of skin cancers and warts.

A more recent addition to the armamentarium of plant-derived chemotherapeutic agents is the class of molecules called taxanes. Paclitaxel (taxol) initially was isolated from the bark of *Taxus brevifolia* Nutt. (Taxaceae). The various parts of *T. brevifolia* and other Taxus species (e.g. *T. canadensis* Marshall, T. baccata L.) were used for the treatment of some non-cancerous condition while the leaves of T. baccata are used in the traditional Asiatic Indian (Ayurvedic) medicine system, with one reported use in the treatment of "cancer". Paclitaxel is used in the treatment of breast, ovarian and non-small-cell lung cancer (NSCLC), and has also shown efficacy against Kaposi sarcoma. Paclitaxel has also attracted attention in the potential treatment of multiple sclerosis, psoriasis, and rheumatoid arthritis. Docetaxel, an active paclitaxel analog, is primarily used in the treatment of breast cancer and NSCLC. Another important addition to the anti-cancer drug armamentarium is the class of clinically-active agents derived from camptothecin, which is isolated from the Chinese ornamental tree, Camptotheca acuminata Decne (Nyssaceae), known in China as the tree of joy. The extract of C. acuminata was the only one of 1000 of these plant extracts tested for anti-tumor activity which showed efficacy and camptothecin was isolated as the active constituent. Later, camptothecin was found to act by selective inhibition of topoisomerase I, involved in cleavage and reassembly of DNA [17]. The two more effective camptothecin derivatives, Topotecan and Irinotecan are now in clinical use. Among these, Topotecan is used for the treatment of ovarian and small-cell lung cancers, while Irinotecan is used for the treatment of colorectal cancers. All of these natural products have led to significant biological discoveries related to their unique mechanisms of action. The well-known plant-derived anticancer drugs in clinical use (or development) are listed in table 2.

Table 2. Representative Plant-Derived Anticancer Drugs in Clinical Use or Development

Drug Class	Example	Source Plant	Collection/Source Region	Development Stage	Mechanism of Action
Vinca alkaloids *	Vinblastine, Vincristine, Vinorelbine	Catharanthus roseus	The Philippines, Jamaica, Madagascar	Clinical use	Binds to tubulin inhibiting microtubule and mitotic spindle formation. Cells arrested in M-phase and cell division stopped.
Lignans*	Etoposide, Teniposide	Podophyllum species	Eastern United States, Himalayas	Clinical use	Stabilizes the topoisomerase II-DNA complex resulting in irreversible double strand break, lethal to cells in S and G2 phases.
Taxanes*	Paclitaxel, Docetaxel	Taxus species	Northwest United States, Europe	Clinical use	Causes tubulin stabilization.
Camptothecins*	Topotecan, Irinotecan HCl	Camptotheca acuminata	China	Clinical use	Binds reversibly to inhibit nuclear topoisomerase I and stabilizes the topoisomerase-DNA covalent complex.
Cephalotaxanes	Homoharringtonine	Cephalotaxus harringtonia	China	Clinical trials	Inhibits protein synthesis at the level of chain initiation and induce differentiation of promyelocytic leukemia cells *in vitro*.
Flavones	Flavopiridol (synthetic based on rohutikine)	Dysoxylum binectariferum	India	Clinical trials	Inhibits phosphokinases and induces topoisomerase II-mediated apoptosis.
Stilbenes *	Combretastatin prodrug (AVE8062A)	Combretum caffrum	South Africa	Clinical trials	Causes mitotic arrest by inhibiting tubulin polymerization.

Chemotherapy for cancer prevention

Chemoprevention is one of the promising strategy for cancer prevention nowadays which involves pharmacological intervention with naturally occurring and synthetic agents alone or in combination to reverse, suppress, or prevent cancer in human beings. Cancer chemoprevention was first defined as ‘‘a strategy of cancer control by administration of synthetic or natural compounds to reverse or suppress the process of carcinogenesis’’ [19]. Cancer is a multistage process by which a normal cell is transformed into a cancerous cell which involves initiation by DNA damaging agents, promotion during which cell proliferation is increased, and progression which involves additional genetic alterations. Chemoprevention strategies target each of these steps including anti-initiation strategies (e.g., DNA repair, detoxification, free-radical scavenging, and carcinogen metabolism) and anti-promotion/anti-progression strategies (e.g., free-radical scavenging, proliferation suppression, differentiation induction, immunity enhancement, inflammation reduction, increase in apoptosis, altered gene expression, and decrease in angiogenesis)[20,21]. Because cancer chemoprevention is designed to occur prior to the onset of cancer diagnosis, little to no toxicity can be tolerated. As such, herbal medicines, botanicals, dietary supplements, and edible plants have all been suggested as

potentially important in cancer chemoprevention due to their long history of human consumption for health purposes [22,-24]. Considerable scientific evidence has suggested that plant-based dietary agents can inhibit the process of carcinogenesis effectively [25].

Cancer cells frequently and possibly invariably possess apoptotic defects. The induction of apoptosis is a primary cytotoxic mechanism of many anticancer agents. Apoptosis is programmed cell death and a highly organized physiological mechanism to destroy injured or abnormal cells. The natural substance either in the form of crude extracts or their isolated components has been recognized to have the ability to induce apoptosis in various tumor cells of human origin. The induction of apoptosis in tumor cells is considered very beneficial in the treatment and prevention of cancer. The apoptotic pathways thus provide exciting molecular targets for new therapeutic agents to specifically promote apoptosis of cancer cells and eventually lead to innovative mechanism-based anticancer drug discovery. Subsequently, apoptosis in recent years has become a challenging issue in biomedical research as the life span of both normal and cancer cells within a living system is regarded to be significantly affected by the rate of apoptosis. Chemopreventive agents that can modulate apoptosis may be able to affect the steady-state cell population, which can be useful in the management and therapy of cancer [26]. In fact, in recent years, certain chemopreventive agents, such as tea polyphenols [27], curcumin [28], and resveratrol [29], have been shown to induce apoptosis. Therefore, it is reasonable to assume that the chemopreventive agents that have proven effects in animal tumor bioassay systems and/or human epidemiology on one hand and cause induction of apoptosis of cancer cells, on the other hand, may have wider implications for cancer control. Taken together, when the events in the progression of a normal cell to a malignant lesion, as depicted in figure 1, are considered many targets can be visualized that can serve as windows of opportunity for chemoprevention of cancer. These opportunities involve both inhibition and induction of pathway(s) by chemopreventive agents. The majority of these agents have a unique function and distribution, and thus their bioavailability differs within the body. In addition, even if a specific agent may play a definitive role in cancer prevention, the synergistic/additive effects of another agent working through a similar or different mechanism(s) may enhance the efficacy in a positive manner.

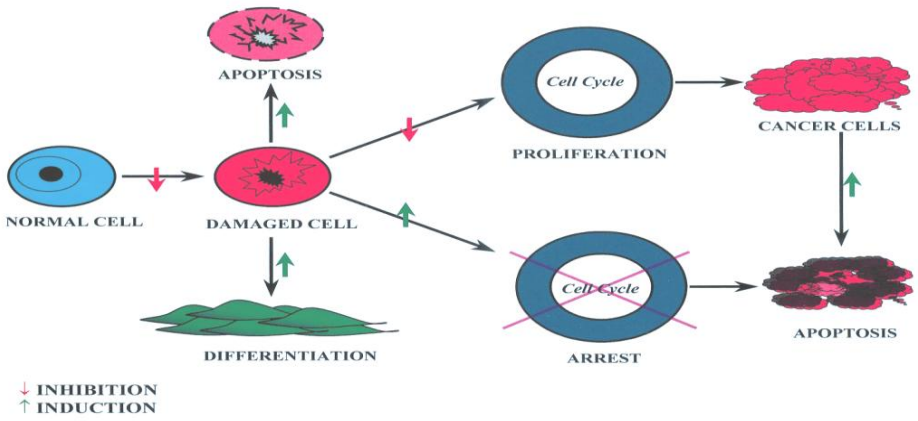

Fig. 1 Development of a normal cell to malignant cell by perturbed cell cycle leading to apoptosis.

Anticancer Activity of Medicinal Plants

A large number of medicinal preparations are recommended for the treatment of cancer in the modern and traditional system of medicine [30, 31]. Conventional medicine is pursuing the use of natural products such as medicinal plants to provide support to the cell on a daily basis to revitalize the normal cell to treat cancer. Herbal drugs are rapidly becoming popular in recent years as an alternative therapy [32]. The traditional medicine refers to a broad range of ancient, natural health care practices, including folk/tribal practices as well as Ayurveda, Siddha, and Unani.

In India, around 20,000 medicinal plants have been recorded. However, traditional communities are using only 7,000 - 7,500 plants for curing different diseases [33]. The total turnover was 48.9 million US $ herbal products in 1999-2000 and now it is around 80 million $ [34]. There are numerous plants and polyherbal formulations claimed to have anticancer activities. In India, more than 87 medicinal plants are used in different combinations in the preparation of 33 patented herbal formulations. Herbal plants contain a lot of antioxidants to control the oxidative stress caused by free radicals. Liver protective herbal drugs contain a variety of chemical constituents like flavonoids, tannins, coumarins, lignans, essential oil, monoterpenes, carotenoids, glycosides, organic acids, lipids, alkaloids and xanthines which have been investigated[35,36]. Medicinal plants continue to play a central role in the healthcare system of large proportions of the world's population [37]. Among the human diseases treated with medicinal plants, cancer is probably the most important genetic disease. Keeping the significance of natural products as a major source of anticancer agents in this review, there are few reputed medicinal plants have been popularly used to explore and identify promising anticancer natural isolate(s) that may be useful for the management and treatment of cancer.

Allium sativum

Allium sativum L. garlic is among the oldest of all cultivated plants being used as a food, having a unique taste and odor along with some medicinal qualities. Modern scientific research has revealed that the wide variety of dietary and medicinal functions of garlic can be because of the sulfur compounds present in it. The compound allicin, methyl allyl trisulfide, and diallyl trisulfide have antibacterial, antithrombotic, and anticancer activities respectively [38]. It is a remarkable plant, which has multiple beneficial health effects such as hypolipidemic, antiarthritic, antimicrobial, antithrombotic, hypoglycemic and antitumor activities. Different garlic preparations including fresh garlic extract, aged garlic, garlic oil and a number of organo sulfur compounds derived from garlic shown to have chemopreventive activity. The chemopreventive activity has been attributed to the presence of organo sulfur compounds in garlic. The two major compounds in aged garlic, S-allylcysteine and S-allylmercapto-L-cysteine possess the highest radical scavenging activity. In addition, S-allylcysteine has been found to reduce the growth of chemically induced and transplantable tumors in animal models. Therefore, the use of garlic may provide some kind of protection from cancer development [39].

Artemisia capillaries

Artemisia capillary is a major food and medicinal resource plan found in Korea. The methanol extracts of Artemisia capillaries were used for the evaluation of DPPH (2,2-diphenyl- 1-picrylhydrazyl) scavenging, total phenolic content, total flavonoid content, hydroxyl radical (OH) scavenging, reducing power assay as antioxidant activity, as well as anticancer activities using MTT assay. As a result, the Artemisia capillaries extracts exhibited potential antioxidant activity and anticancer activity *in vitro*. These results suggest that the *Artemisia capillaries* extracts have a potential alleviated oxidation process, cell motility activity, and tumorigenesis [40].

Aeginetia indica L

Aeginetia indica L., a parasitic plant, an extract was investigated for the antitumor activity. BALB/c mice, inoculated 100000 syngeneic Meth A tumor cells (*i.p.*), were administered 2.5 mg/kg of A. indica extract, *i.p.* every 2 days from day 0. The untreated mice died of an ascetic form of tumor growth within 21 days, whereas all the treated mice completely recovered from tumor challenge without any side effects. The extract did not exert direct cytotoxic activity against Meth-A *in vitro* [41].

Andrographis paniculata

Andrographolide, the major di-terpenoid of the Andrographis paniculata extract has shown cytotoxic activity against KB (human epidermoid carcinoma) and P-388 (lymphocyte leukemia) cells. The methanol extract of aerial parts of Andrographis paniculata and some of the isolated compounds showed growth inhibitory and differentiating activity on M1 (mouse myeloid leukemia) cells [42].

Alpinia katsumadai

7, 8-Dihydroxyflavonone, isolated from the seeds of Alpinia katsumadai, was found to have cytotoxic effect against A-549 and K-562 [43]. Sesamolin, obtained from the sesame seeds, inhibited the growth of human leukemia HL-60 cells in cultures and the synthesis of macromolecules in dose and time dependent manners. Also, the inhibitory effect of Sesamolin on DNA synthesis was irreversible [44].

Aglaia sylvestris

Silvestrol was first isolated from the fruits of *Aglaia sylvestris* (M. Roemer) Merrill (Meliaceae).The chloroform-soluble extract was found to be cytotoxic to several human cancer cell lines and, more importantly, the extract was active in the P-388 *in vivo* test system. Silvestrol was cytotoxic against lung (Lu1), prostate (LNCaP), and breast (MCF-7) cancer cells as well as against umbilical vein endothelial cells (HUVEC) and exhibited dose-dependent cytotoxicity with no significant weight loss. It also showed activity when administered intraperitoneally twice daily for 5 days in the P-388 murine leukemia model [45].

Beta vulgaris

In vitro inhibitory effect of *Beta vulgaris* (beet) root extract on Epstein-Barr virus, early antigen (EBV-EA) was evaluated. The result showed a high order of activity compared to capsanthin, cranberry, red onion skin, and short and long red bell peppers. An *in vivo* anti-tumor activity evaluated against the mice skin and lung bioassays. Result also revealed a significant tumor inhibitory effect. The combined findings suggest that Beta vulgaris (beetroot) ingestion can be one of the useful means to prevent cancer [46].

Boerhaavia diffusa

Boerhaavia diffusa (Linn.) (Syn. B. repens L.; B. procumbens Roxb) commonly known as "Punarnava" in Indian system of medicine is a perennial creeping herb belongs to family Nyctaginaceae. Its ethanol extract showed a cytotoxic effect against Hela cell lines and inhibit the S-phase of the cell cycle. It also inhibits the growth of cancer cells in DMBA- induced cancer carcinogenesis in mice through free radical scavenging mechanism [47].

Buplevuum

Saikosaponin D, a saponin extract derived from several species of *Buplevuum* (umbellifereae), and is used for the treatment of various liver diseases in traditional Chinese medicine. It is reported that Saikosaponin D inhibits the cell growth of human cancer cell line A-549 and provides a molecular understanding of this effect. The results showed that the Saikosaponin D inhibited the proliferation of A-549 by inducing apoptosis and blocking cell cycle progression in G1 phase [48].

Bambyx arundinacea

Polysaccharopeptide, isolated from edible mushroom *B. arundinacea*, is a herbal medicine known for its anti-angiogenesis properties. The expression of vascular endothelial growth factor in this tumor

was suppressed which shows that anti-angiogenesis should be one of the pathways through which polysaccharide peptides mediates its antitumor activity [49]. Swiss albino mice inoculated with Ehrlich Ascites Carcinoma were treated with the extract of *Bambyx arundinace*, and also with clinically highly effective drug bleomycin. The significant tumor cell growth inhibition was observed using the extract of B. arundinacea [50].

Camellia sinensis

Green tea is an aqueous infusion of dried unfermented leaves of *Camellia sinensis* (Family Theaceae) possesses numerous biological activities including antimutagenic, antibacterial, hypocholesterolemic, antioxidant, antitumor and cancer preventive activities. It has been reported that green tea leaves contain six compounds (+)-gallocatechin (GC), (-)-epicatechin (EC), (-)-epigallocatechin (EGC), (-)-epicatechin gallate (ECG), (-)-epigallocatechin gallate (EGCG) and caffeine. These compounds were tested against four human tumor cells lines such as (MCF-7 breast carcinoma, HT-29 colon carcinoma, A-427 lung carcinoma, and UACC-375 melanoma). EGCG, GC, and EGC found to be most potent against all four tumor cell lines. In view of these extensive *in vitro* studies, it would be of considerable interest to evaluate all three of these components in animal tumor model systems before final decisions are made concerning which of these potential chemopreventive agents should be taken into broad clinical trials [51].

Camptotheca acuminate

Camptothecin (CPT) is an anticancer and antiviral alkaloid isolated from Chinese tree *Camptotheca acuminata* (Nyssaceae). Several attempts have been made to produce CPT from cell suspensions. The hairy roots of Camptotheca acuminata produce and secrete Camptothecin as well as the more potent and less toxic natural derivative, 10- hydroxycamptothecin, into the medium [52].

Cucurbita maxima

In vivo methanol extract of the aerial part of *Cucurbita maxima* was studied for anticancer activity against Ehrlich ascites carcinoma cells in mice. Oral administration of the methanol extract of the Cucurbita maxima at a dose of 200 mg/kg and 400 mg/kg give the cytotoxicity against the Ehrlich ascites carcinoma cells in mice in dose-dependent manner [53].

Citrus maxima

The methanol extract of the leaves of the *Citrus maxima* was evaluated for its anticancer activity at a dose of 200-400mg/kg against Ehrlich Ascites carcinoma cell lines in Swiss albino mice. Oral administration of the methanol extract of the leaves of Citrus maxima reverses the tumor parameters such as tumor volume, viable tumor cell count, and increase body weight, hematological parameters, and life span. Therefore study shows that methanol extract of the aerial part of Citrus maxima possesses antitumor activity in a dose-dependent manner [54].

Curcuma longa

Anticancer potential of the rhizomes of turmeric (*Curcuma longa*) was evaluated *in vitro* using tissue culture methods and *in vivo* in mice using Dalton's lymphoma cells grown as ascites form. *C. longa* extract inhibited the cell growth in Chinese Hamster Ovary (CHO) cells at a concentration of 0.4 mg/ml and was cytotoxic to lymphocytes and Dalton's lymphoma cells at the same concentration. Cytotoxic effect happened within 30 min at room temperature (30oC). Curcumin was found to be the active constituents of C. longa which showed cytotoxicity to lymphocytes and Dalton's lymphoma cells at a concentration of 4 mg/ml. Initial experiments indicated that *C. longa* extract and curcumin reduced the growth of animal tumors [55]. *Cynara syriaca* and *Cynara cardunculus*: Apoptotic and cytotoxic activity of plant extracts obtaining from *Cynara syriaca* in and *Cynara cardunculus* (artichoke species) against DLD-1 colorectal cancer cells was determined. This paper was the first report, concerning with, positive effects of plant extracts obtained from two different artichoke

species against to colorectal cancer cell line. In this study, their results demonstrated that artichoke extracts had inhibitory effects on the proliferation of human colorectal cancer DLD-1 cells. Extracts not only hold back cell proliferation but also induce apoptotic

Croton cajucara

The effects of two nor-diterpenes, trans-dehydrocrotonin and trans-crotonin (DCTN) from *Croton cajucara* (Euphorbiaceae), on the survival of mice bearing Sarcoma 180 and Ehrlich carcinoma ascitic tumors, on the proliferation of cultured Ehrlich cells and TNF alpha activity were determined. A significant TNF alpha activity was detected in Ehrlich tumor-bearing mice treated with DCTN suggesting an enhanced immune function. No apoptosis was seen on *in vitro* electrophoresis of DNA extracted from the tumor cells treated with DCTN and CTN [56].

Cedrus deodara

AP9-cd, a standardized lignan composition from *Cedrus deodara* consisting of (-) -wikstromal, (-)-matairesinol, and dibenzyl butyrolactol, showed cytotoxicity in several human cancer cell lines. It inhibited Molt-4 cell proliferation with IC50 of ~15µg/ml, increased sub-G0 cell fraction with no mitotic block, produced apoptotic bodies and induced DNA ladder formation. Annexin V-FITC/PI-stained cells showed a time-related increase in apoptosis and post-apoptotic necrosis. All these biological end-points indicated cell death by apoptosis. Persistently, high levels of NO and peroxide appeared to decrease mitochondrial membrane potential (Ψmt). AP9-cd caused 2-fold activation of caspase-3 in MOLT-4 and 5-fold activation in HL-60 cells. Also, caspases-8 and -9 were activated in HL-60 cells. Bhushan et al.,[57] studies indicated that AP9-cd mediated early NO formation leads to caspases activation, peroxide generation, and mitochondrial depolarization which may be responsible for mitochondrial-dependent and -independent apoptotic pathways involved in the killing of leukemia cells by AP9-cd. The *in vivo* anticancer activity of Cedrus deodara was studied using Ehrlich ascites carcinoma and colon carcinoma (CA-51) models in mice [58]. The tumor regression observed with Ehrlich ascites carcinoma and CA-51 was 53 % and 54 %, respectively, when AP9-cd was given at 300 mg/kg, i.p. for nine days in the Ehrlich ascites carcinoma bearing mice and 400 mg/kg, i.p. for the same period in the CA-51 model. It was comparable with 5-fluorouracil at 22 mg/kg and 20 mg/kg, respectively.

Cymbopogon flexuosus

An essential oil from a lemongrass variety of *Cymbopogon flexuosus* induce apoptosis in human leukaemia HL-60 cells. C. flexuosus oil inhibit cell proliferation with the IC50 value of 30 µg/ml and induces strong and early apoptosis as measured by various end-points, e.g. annexin V binding, DNA laddering, apoptotic bodies formation and an increase in hypo-diploid sub-G0 DNA content [59].

Dillenia pentagyna

Rosangkima and Prasad, studied the antitumor activity of *Dillenia pentagyna* against murine ascites Dalton's lymphoma (DL) *in vivo* [60]. The methanolic extract showed maximum activity. The protein concentration in liver and DL cells decreased mainly at 96 h of treatment. The natural product of this plant promises to be more active against DL than others and the decrease in glutathione level may be one of the important steps in resulting this antitumor effect.

***Erythroxylum pervillei* Baill**

Pervilleine A, along with eight other tropane alkaloids, was isolated from the roots of *Erythroxylum pervillei* Baill. (Erythroxylaceae) collected in southern Madagascar [61]. The chloroform-soluble extract was found to be selectively cytotoxic against a multi-drug resistant (MDR) oral epidermoid cancer cell line (KB-V1) in the presence of the anticancer agent vinblastine. The pervilleines were isolated using bioassay-guided fractionation including silica gel chromatography and aluminum oxide chromatography. *Pervilleine* A was selectively cytotoxic against KB-V1 in the presence of

vinblastine. Further *in vitro* studies related to the MDR inhibition were undertaken in comparison with existing MDR agents including verapamil. *Pervilleine* A was then tested in the *in vivo* hollow fiber model with promising results indicating that it may be more effective than verapamil for reversing MDR [62].

Glycyrrhiza glabra

Licochalcone (LA) is a novel estrogenic flavonoid isolated from *Glycyrrhiza Glabra* showed significant antitumor activity in various malignant human cell lines. Evaluation of its anti-cancer activities were carried out in LA-elicited growth control and induction of apoptosis using androgen-independent p53-null PC-3 prostate cancer cells. Licochalcone induced a modest level of apoptosis but had a more pronounced effect on cell cycle progression arresting cells in G2/M, accompanied by suppression of cyclin B1 and cdc2. It also inhibited phosphorylation of Rb, decreased expression of transcription factor E2F concurrent with reduction of cyclin D1, down-regulation of CDKs 4 and 6, but increased cyclin E expression. These findings provide a mechanistic explanation for Licochalcone activity and suggest that it possess chemopreventive potential and its anticancer effect should be further explored [63].

Glinus lotoides

The antitumor activity of the methanolic extract of *Glinus lotoides* has been evaluated against Dalton's ascitic lymphoma in Swiss albino mice. A significant enhancement of the mean survival time of tumor-bearing mice and peritoneal cell count in normal mice was observed with respect to the control group [64].

Hypericum perforatum

Black Cohosh is a well known herbal remedy of long traditional use against menopausal complaints. Isopropanolic extract of black cohosh on an animal model of endometrial adenocarcinoma was evaluated for incidence and localization of metastasis, partly in the setting of a combination treatment with tamoxifen. In contrast to the endometrial estrogen against tamoxifen, black cohosh didn't show further growth or metastasis in the primary tumor [65].

Hypericum perforatum

Hypericin, a powerful naturally occurring photosensitizer, is found in *Hypericum perforatum*, commonly known as St. John's wort. In recent years increased interest in hypericin as a potential clinical anticancer agent has arisen since several studies established its powerful *in vivo* and *in vitro* antineoplastic activity upon irradiation. Investigations of the molecular mechanisms underlying hypericin photocytotoxicity in cancer cells have revealed that this photosensitizer can induce both apoptosis and necrosis in a concentration and light dose-dependent fashion. The antiproliferative effect of selective serotonin reuptake inhibitors (SSRIs) and serotonin antagonists has been demonstrated in prostate tumors. Since its components act as serotonin reuptake inhibitors and exert cytotoxic effects on several human cancer cell lines, the treatment analysis of this extract on the growth of human prostate cancer cells *in vitro* and *in vivo* were studied and it highlights a significant reduction of tumor growth and metastasis suggesting that this natural compound may be useful in the treatment of prostate cancer [66]. Moreover, PDT with hypericin results in the activation of multiple pathways that can either promote or counteract the cell death program. The *in vivo* antitumor activity of the natural photosensitizer hypericin was evaluated by Cavarga et al.,[67].

Lithospermum erythrorhizon

"b-Hydroxy isovaleryl shikonin (HIVS), which was isolated from roots of the plant, *Lithospermum erythrorhizon* induces apoptosis in various human tumor cells. Suppression of the activity of PLK-1(polo-like kinase 1) via inhibition of tyrosine kinase activity by b- HIVS might play an important role in the induction of apoptosis [68].

Maclura aurantiaca and Epilobium hirsutum

Primary screening of alcoholic extracts of fruits of *Maclura aurantiaca* (Moraceae) and the overground part of *Epilobium hirsutum* (Onagraceae) was conducted in order to test the anti-tumor action. Applied in doses of 100 mg/kg and 90 mg/kg, Maclura extract increased the life span of the mice by 158 and 152% respectively in P-388 and ascitic tumor of Ehrich. In doses of 1 mg/kg and 3 mg/kg, the Epilobium extract prolonged the life span of the mice by 156 and 158% respectively in P-388 and ascitic tumor of Ehrlich [69].

Momordica cochinchinensis

The antitumor activity of the crude water extract from Gac fruit (*Momordica cochinchinensis*) was investigated *in vivo* and *in vitro*. The water extract inhibited the growth of the colon 26-20 adenocarcinoma cell line, transplanted in Balb/c mice, reducing wet tumor weight by 23.6%. Histological and immunohistochemical results indicated that Gac water extract reduced the density of blood vessels around the carcinoma. The water extract also produced a marked suppression of cell proliferation in colon 26-20 and Hep-G2 cells. Cell cycle analysis demonstrated a significant accumulation of cells in the S phase by water extract [70].

Nigella sativa

Anticancer activity of the methanol extract of the seeds of Nigella sativa was evaluated by MTT assay on different cancer and normal cell lines such as HL-60, U-973 AND HEK 293T. It was demonstrated by the result that methanol extract of the *Nigella sativa* seeds possesses potent inhibitory activity against Hl-60 and U-937 cell lines [71].

Parthenium hysterophorus

The methanol and acetone extract of the flowers of *Parthenium hysterphorus* were studied for *in vitro* anticancer activity against the A-549 (Lung adenocarcinoma) cell lines by MTT assay and Tryphan blue exclusion assay. In this study, result shows that acetone extract of Parthenium hysterphorus give greater anticancer activity compare to methanol extract [72].

Psoralea corylifolia

Psoralea corylifolia seed extract has been found to stimulate the immune system in mice. Administration of the extract was found to inhibit EAC ascitic tumor growth and stimulate natural killer cell activity, antibody dependent cellular cytotoxicity, antibody-forming cells, and the antibody complement-mediated cytotoxicity during tumor development [73].

Solanum nigrum

Solanum nigrum Linn. belongs to family Solanaceae commonly known as black nightshade, Makoy and deadly nightshade. It possesses no. of medicinal properties like antimicrobial, anti-oxidant, cytotoxic properties, antiulcerogenic, and hepatoprotective activity. *Solanum nigrum* is a potential herbal alternative as an anti-cancer agent and its one of the active principle Diosgenin reported to be responsible for this action. A Hela cell is an immortal cell line used in medical research. The cell line was derived from cervical cancer cells of Henrietta Lacks, who died from her cancer in 1951. At first, the cell line was said to be named after a “Helen Lane” in order to preserve Lacks’s anonymity. Anticancer activity of *Solanum nigrum* was evaluated. The methanol extract of the fruit of *Solanum nigrum* was tested for its inhibitory effects on the Hella cell line and vero cell line by SRB assay and MTT assay in a concentration range between 10mg/ml to 0.0196mg/ml. Both the assay shows significant cytotoxic effects on the Hella cell line and little effect on Vero cell line [74]. This shows that *Solanum nigrum* may indeed have potential as an anticancer herb.

Saussurea lappa

Bioassay-directed fractionation of *Saussurea lappa* led to the isolation of a novel lappadilactone and seven sesquiterpene lactones as cytotoxic principles against selected human cancer cell lines.

Lappadilactone, dehydrocostuslactone, and costunolide exhibited the most potent cytotoxicity against Hep-G2, OVCAR-3 and HeLa cell lines [75].

***Semecarpus anacardium* Linn**

The effect of *Semecarpus anacardium* Linn. Nut milk extract on host detoxification system in aflatoxin B1 induced hepatocellular carcinoma, which is a vital mechanism in cancer treatment, was studied in male albino rats by Premalatha and Sachdanandam, [76]. The nut extract affords anticancer activity by enhancing both phase I and phase II enzymes to near normal levels and they investigated that, much of the anticarcinogenic potency of this nut extract on aflatoxin B1-induced hepatocarcinogenesis is mediated through the induction of hepatic biotransformation enzyme.

Solanum pseudocapsicum

Beldame et al. [77], tested the total alkaloid fraction of the methanolic extract of *Solanum pseudocapsicum* leaves for it's *in vivo* antitumor activity against Dalton's Lymphoma Ascites model in mice. The total alkaloid fraction at 2.5 and 5.0 mg/kg body weight doses exhibited antitumor activity as revealed by the significant increase in the mean survival time and the percentage increase in life span of tumor-bearing mice. The antitumor activity observed may be due to its cytotoxic properties. However, the treatment caused a significant decrease in body weight, below the normal, indicating the toxicity of the treatment.

Sorbaria sorbifolia

Sorbaria sorbifolia ethyl acetate extract containing the compounds 5, 2', 4'-trihydroxy-6, 7, 5'-trimethoxyflavoney and succinic acid improved the immune function and strengthen antitumor effect in sarcoma-180 [78].

Vitis vinifera

Proanthocyanidins (PAs), also known as condensed tannins, are naturally occurring oligomers and polymers of flavan-3-ol monomer units widely found Grape seeds (*Vitis vinifera* L.) which have been used as nutritional supplements and, as antioxidants, to prevent atherosclerosis and cardiovascular diseases. Proanthocyanidins show the antimutagenic activity. Antitumor and antioxidant activity of ethanolic extract of *Vitis vinifera* L. leaves were evaluated against Ehrlich ascites carcinoma (EAC) induced in Swiss albino mice. The antitumor effect and antioxidant role were determined by using tumor volume, packed cell volume and estimation of liver LPO and antioxidant enzymes such as SOD, CAT. Treatment with extract at a dose of 200 and 400 mg/kg increased mean survival time, decreased the levels of LPO and increased the levels of superoxide dismutase, catalase. The results suggest that ethanolic extract of *Vitis vinifera* exhibited significant antitumor, an antioxidant response in EAC tumor-bearing mice [79].

Withania somnifera Dunal

Withania somnifera, popularly known as Ashwagandha in India, along with paclitaxel was evaluated for the antioxidant and anticarcinogenic activity in Benzo(a)pyrene(B(a)P)-induced small cell lung cancer in Swiss albino mice shows that Withania somnifera along with paclitaxel is a novel approach to treat small cell lung cancer. The ethanolic extract of roots was tested against Dalton's ascitic lymphoma in Swiss albino mice. A significant increase in the life span and decrease in the number of cancer cells and tumor weight were noted in tumor-induced mice after treatment which suggests of protective action in Dalton's ascitic lymphoma [80].

***Ziziphus mauritiana* Lam**

Betulinic acid, a pentacyclic triterpene, is a common secondary metabolite of plants, primarily from Betula species (Betulaceae). Betulinic acid was isolated from *Ziziphus mauritiana* Lam. (Rhamnaceae) collected in Zimbabwe (Pisha et al., 1995). The ethyl acetate-soluble extract displayed selective cytotoxicity against human melanoma cells (MEL-2). Betulinic acid was isolated using

bioassay-guided fractionation including silica gel chromatography and crystallization techniques. This compound was selectively cytotoxic against several human melanoma cancer cell lines (MEL-1, MEL-2, MEL-4). Betulinic acid was then found to be active *in vivo* using athymic mice carrying human melanomas, with little toxicity. Further biological studies indicated that betulinic acid induces apoptosis [81].

Conclusion

Medicinal plants have been used for the cure of different ailments including cancer for thousands of years. Large numbers of medicinal plants having anticancer properties are available in nature but they are not fully phytochemically investigated.[It should be of particular interest to explore the anticancer potential of the medicinal plant's extracts for isolation and characterization of the active anticancer principles so that better, safer and cost-effective drugs can be developed for treating cancer. Phototherapy is cost effective and easily available to the people, so comprehensive programme of identification, evaluation, preparation, and cultivation of medicinal plants should be encouraged to promote proper use of traditional medicine. The universally current review provides splendid support for the role of plant-mediated drug as combating strategies against cancer treatment in the chronic stage. A comprehensive review was conducted to assess the safety and efficacy of herbal medicines commonly used by patients in an attempt to prevent cancer, treat cancer and adverse effects associated with conventional cancer treatments.

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