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International Journal of Current Research
Vol. 5, Issue, 07, pp.1908-1919, July, 2013

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

REVIEW ARTICLE

HERBAL REMEDIES TO COMBAT CANCERS IN HUMANS AND ANIMALS – A REVIEW

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ARTICLE INFO

Article History:
Received 06th April, 2013
Received in revised form
24th May, 2013
Accepted 16th June, 2013
Published online 18th July, 2013

Key words:
Ayurveda,
Cancer,
Herbs,
Treatment.

ABSTRACT

Cancer is considered as one of the leading cause of death worldwide, especially in the economically developed countries. Over 12.7 million cancer cases with the death tolls reaching up to 7.6 million were in 2008 throughout globe. The situation is no any different in a country like India where death toll per year reaches upto 5.8 lakhs out of the 8.5 lakhs diagnosed clinical cases. Conventional therapies based on surgery, radiation therapy, chemotherapy, hormone therapy, immunoadjuvant therapy, cryotherapy, apoptin therapy and nanoparticles (to facilitate better drug delivery) are widely used but are having side effects, resulting in fatal outcome. Under such circumstances, herbal therapy forms an integral part of the alternative approach as they are cheaper and are without having any toxic effect. More than 50% of all modern drugs in clinical use are herbal products, many of them having the ability to control cancer and importantly, over 60% of cancer patients use them. Plants are used against various types of tumors/cancers such as sarcoma, lymphoma, carcinoma and leukemia. Natural non-steroidal anti-inflammatory substances and their roles to prevent cancer need to be explored. Broadly, the anticancer mechanisms of herbs have been divided into two distinct categories viz. direct cytotoxicity and immunomodulation. Several herbs add to the versatility of cancer management by boosting up the immune system and thereby, preparing the body to defend against future or existing cancer and include *Morinda citrifolia, Catharanthus roseus, Taxus brevifolia, Camptotheca acuminate, Podophyllum species, Tinospora cordofolia, Glycyrrhiza glabra* etc. having promising anticancer properties. India is an abode of several botanical plants effective against tumours of brain and uterus; abdomen and glandular organs; throat and breast cancer. Thus, it is anticipated that plants can provide potential bioactive compounds for the development of new therapies to combat cancer. But their efficacy in humans and animals need to be evaluated. Thus, rigorous safety and quality evaluation, comparative clinical studies using modern techniques, proper standardization methods, and good manufacturing practices are extremely important. Isolation and purification of biologically active components from the bulk extracts need to be carried out side by side to understand the basic mechanisms of the drug action. All these form the topic of discussion of this review in order to find out solution to this grave disease of mankind and animals without causing much stress and side effects.

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INTRODUCTION

Cancer is one of the most dreadful diseases of human as well as animals. It stands as second leading cause of death in economically developed countries (following heart diseases) and third leading cause of death in developing countries (following heart and diarrhoeal diseases). In an estimate, it affected 12.7 million persons and death around 7.6 million people in 2008 around the globe and the status can be imagined with the statistics that well trained and equipped country like United states is expecting approximately 1,660,290 new cancer cases with and 580,350 cancer deaths in 2013 (www.cancer.org). According to another previous report, about 24.6 million persons live with cancer, about 10.9 million cases per year are diagnosed and more than 6.7 million deaths are recorded (Parkin *et al*., 2002). Cancers of prostrate; breast; colon and skin are the most common forms in man and animals. Breast cancer is the most common form of cancer in women worldwide (Koduru *et al*., 2007). Second most cause of cancer deaths in is the colon cancer. In the U.S, 37, 000 deaths occur each year due to prostate cancer (second to skin cancer) out of 180,000 newly diagnosed cases (American Cancer Society, 1999). In a developing nation like India, cancer is a grave cause of human death, the toll rising upto 5,80,000, out of 8,50,000 new cases, majority of which are due to oral, lung and stomach cancer (in male) and breast and cervical cancer (in female) (Dhanamani *et al*., 2011).

The remedies of deadly diseases like cancer/ neoplasia in addition to AIDS, and any other haematological or autoimmune disorders is yet to be discovered. Neoplasia as such can be defined as "growth of new cells that occurs without control (malignancy), serves no useful function, and has no orderly arrangement". Cancer is the second leading cause of death in economically developed countries (following heart diseases) and the third leading cause of death in developing countries (following heart and diarrhoeal diseases), thereby creating challenges in the way of treatment (Kutluk and Kars, 1998; Hoyert *et al.*, 2005). The major cancer causing agents are dietary imbalances, obesity, smoking, chronic inflammation and hormones (Ames and Gold, 1995). Researchers and scientists of various disciplines are making their best efforts for discovering the cure of this disease by surgery, radiation therapy, chemotherapy, hormone therapy, immunotherapy and cryotherapy but with highly inconsistent and ill-defined results (Yarney *et al*., 2013). There are lots of side effects of chemotherapy and radiotherapy that makes the

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patient even worse than the cancer itself (Tucker *et al*., 1977). Sophisticated therapeutic strategies in modern medicine, though effective, but affect humanity and do not reach all sections of human populations in all corners of the world due to the problems of affordability and as a consequence, large number of human populations however still depends up on plant based traditional alternative systems of medicine to combat debilitating diseases. Plants have long been used for treating the cancer patients (Wargovich *et al*., 2001). Recently, there is a great emphasis on the use of alternative or complementary medicine for the treatment of cancer due to their low toxicity and costs especially employing the plants and herbs, fruits and vegetables, panchgavya element of cow urine (cowpathy) (Dhama *et al.*, 2005a,b; Mathew *et al*., 2010; Tanaka *et al*., 2011; Umashanker and Shruti, 2011; Jin *et al*., 2012; Mahima *et al*., 2012, 2013a; Sun *et al*., 2012; Tiwari *et al.*, 2012; Dhama *et al*., 2013a,b). More than 270,000 higher plants existing in the world, but only a limited portion has been explored phytochemically (Mahima *et al*., 2012). Many of them however have been screened for anticancer property throughout the world (Hartwell, 1982; Parkin *et al*., 2002; Premalatha and Govindarajan, 2005; Archana *et al*., 2011; Yarney *et al*., 2013). India is a rich source of medicinal plants and number of plant extracts used against diseases in various systems of medicine such as Ayurveda, Siddha and Unani. Ayurveda is the traditional Indian system of medicine from ancient times, mostly using herbal preparations, to prevent or cure various tumors. The first written records on the medicinal uses of plants appeared in about 2600 BC from the Sumerians and Akkaidians. The best known Egyptian pharmaceutical record, "Ebers Papyrus", recorded more than700 drugs, represents the history of Egyptian medicine dated from 1500 BC. Thousands of herbal and traditional compounds are being screened worldwide to validate their use as anti-cancerous drugs (Liu *et al*., 1998; Diwanay *et al*., 2004; Premalatha and Govindarajan, 2005, Vickers, *et al.*, 2006; Paul *et al*., 2011).

THERAPIES FOR CANCER

Depending upon clinical criteria such as, age, type of cancer, size and metastasis patients are roughly divided in to high risk and low risk cases; each risk category follows different system for therapy. When cancer is diagnosed, therapists face a formidable range of challenges. The treatment possibilities are surgery, radiation therapy, chemotherapy, hormone therapy, immunoadjuvant therapy, cryotherapy, cytokine therapy, apoptin and others, inspite of these therapeutic choices, cancer remains a deadly malady associated with high mortality (Natesan *et al*., 2006; Nair *et al*., 2010; Dhama *et al*., 2013c,d). Chemotherapy and radiotherapy are full of side effects making the condition of patients worse than cancer itself (Mann and Dibois, 2004) and there comes the justification of the old proverb saying "Prevention is always better than cure" as there is involvement of high cytotoxic loads and invasive procedures for treating cancer. Recently, apoptin therapy by transfection of anti-sense survivin in skin cancer, silencing the Bmi- 1 gene in breast cancer, use of XIAP antisense oligonucleotides in lung cancer have been used (Sharma *et al*., 2005; Ohnishi *et al*., 2006; Wong, 2011). In the modern days, with the efforts of the scientists and researchers, improvement of the therapeutic potential of anticancer drugs like paclitaxel and doxorubicin have been increased by the use of gold-conjugated and carbon nanoparticles (Minchin, 2008; Allen and Cullis, 2004; Garde, 2012; Hollmer, 2012).

The question mark of side effect still persists. The survivality of patients under the umbrella of conventional therapy is also very much negligible (2.4%). Nevertheless, uncertainty with respect to success of such approach to cancer treatment creates the urge for alternative treatments causing fewer side effects and increase survival rates (Cassileth, 1996; Vickers *et al*., 2006; Paul *et al*., 2011).

HERBAL THERAPY – AN INTEGRAL PART OF ALTERNATIVE APPROACH TO CANCER TREATMENT

The World Health Organization estimates that approximately 80% of the world's inhabitants rely on traditional medicine for their primary health care. Any practical solution in combating cancer is of paramount importance. Herbal medicines maintain the health and vitality of individuals, cures diseases, and also prevents, suppress, or reverse the progression of cancer without causing toxicity. More than 50% of all modern drugs in clinical use are herbal products, lots of which have the ability to control cancer. A recent study showed that over 60% of cancer patients use herbs as therapy (Sivalokanathan and Ilayara, 2005; Madhuri and Pandey, 2008). Enhancing detoxification mechanism of the body is an important function played by many herbs in combating cancer. Inhibition of cancerous growth via modulation of specific hormonal and enzymatic activities is another major mechanism played by herbal biological modifiers. Reduction of side effects that are toxic caused by chemotherapeutic as well as radio therapeutic agents make may herbs beneficial to fight cancer (Nair *et al*., 2010). Many plants are used against various types of tumors/cancers such as sarcoma, lymphoma, carcinoma and leukemia. Attempts are being made to isolate active constituents from natural sources that could be used to treat very serious illness. Recently, a greater emphasis has been given towards the researches on complementary and alternative medicine that deals with cancer management (Ahmed and Bassuony, 2009; Aghsaghali, 2012; Mahima *et al*., 2012; Tiwari *et al*., 2012). Rasayana forms an integral part of Indian traditional medicine and the herbs used in this regard reduce the imbalances of the body. Thus, it has a positive impact on providing protection to the body from the side effects of tumor-specific chemotherapy and radiation therapy (Chakraborty and Pal, 2012). This makes herbal therapy to act as an integral part of alternative approach, in addition to mind-body intervention, nutritional supplements and even bioelectromagnetics (Cassileth *et al*., 2001). The immune system is boosted up by several herbs that prepare the body to defend against future or existing cancer, thereby adding to the versatility of cancer management (Mahima *et al*., 2012, 2013b; Tiwari *et al*., 2012). Herbal preparations can act without possessing a threat of any side effect via a pathway similar to pharmaceuticals. Natural anti-inflammatory compounds are widely distributed in green tea; turmeric and rosemary; feverfew etc thus have increased the need of exploring natural non-steroidal anti-inflammatory substances for their use to prevent cancer (Wargovich *et al*., 2001; Lampe, 2003; Percival *et al*., 2012).

Mechanism of action of herbs

Broadly, the anticancer mechanisms of herbs have been divided into two distinct categories viz. direct cytotoxicity and immunomodulation. Abnormal cell proliferation and the inhibition of apoptois of cells are responsible for causing cancer, being governed by an array of genes. In this regard, the medicinal herbs can modulate some oncogenes, or tumor-suppressor genes. As far as the immunomodulation is concerned, medicinal herbs can potentiate the immune response that has got various therapeutic applications in case of malignancy, the most common ingredient of herbs having immunomodulatory property being polysachharides (Zhu *et al*., 2007). The potential biological and medical efficacy of herbs further necessitates the need to evaluate the efficacies based on molecular mechanisms (Kitagishi *et al*., 2012). There are many proposed means of anti cancer activity but in most of cases of papillomatosis reduction in the frequency of micronuclei is supposed to be because of decrease in total chromosomal aberrations in the formation of centric rings, dicentrics and acentric fragments with exchange, chromatid breaks and breakage of chromosome (Meena *et al*., 2006). This review aims at giving an overview of some of the most important herbal agents with anti-tumor activity.

Classical Examples of Herbs having Anti-Cancer Role

Acacia nilotica

Acacia nilotica (Linn.) is known for its medicinal properties in most of ancient systems. The gum, flower and leaf aqueous extracts of *Acacia nilotica* (Linn.) have been reported to use for the cancer treatment. Similarly, it has been proven to have inhibition of skin

papillomagenesis in male Swiss albino mice. The use of different preparation during the peri- and post initiation periods of DMBA and croton oil application reduced the values of tumor burden, tumor incidence and cumulative number of papillomas. Moreover, significant reduction in the frequency of micronuclei was evident in treatment groups all these were associated with decrease in total chromosomal aberrations in the form of chromatid breaks, breakage of chromosome, centric rings, dicentrics and acentric fragments with exchange (Meena *et al*., 2006; Sakthivel *et al.*, 2012).

Aegle marmelos

Aegle marmelos is commonly known as Bael tree in India, belongs to family *Rutaceae*. The major bioactive component of the plant is lupeol, a tri-terpenoid. It increases the expression of Era gene in MDA-MB-231 Era –negative breast cancer cells and also inhibited cell proliferation. It has anti-cancer activity against primitive neuro ectodermal tumors (PNET), malignant ascites, thyroid cancer and various malignant tumours of brain and spinal cord (Lampronti *et al*., 2003). Pyranocoumarin isolated from the seed gives protection against pylorus ligation and aspirin induced gastric ulcers in rats. It also possesses anti-viral and anti-inflammatory properties.

Aglaila sylvestre

Silvestrol was first isolated from the fruits of *Aglaila sylvestre*, belongs to family *Meliaceae* (Hwang *et al*., 2004), and has selective cytotoxicity against lung and breast cancer cell lines (Cragg and Newman, 2005).

Aloe vera

Aloe vera has been studied on different stages of tumours including 2^{nd} -stage skin carcinogenesis in Swiss albino mice. Oral administration of aloe leaf decreased the number and size of the papillomas. It not only reduced the incidence but also increased the latency period of papillomas in comparison to control groups. Furthermore significant reduction in the level of glutathione, lipid peroxidation levels, DNA, catalase and protein in the skin of mice was observed (Chaudhary *et al*., 2007; Efferth *et al*., 2007).

Alstonia scholaris

Alstonia scholaris contains active principles like alkaloids, flavanoids and phenolic acid. The major chemical components are alstonine, echitamine chloride, villastonine and alkaloids ditamine, echitamine or ditaine, and echitenines (Jagetia and Baliga, 2006). Echitamine chloride has anticancer activity in S-180 and fibro sarcoma (Kamarajan *et al*., 1991). Villastonine has antiamoebic activity and *in vitro* anticancer activity against human lung cancer cell lines MOR-P (adeno carcinoma) and COR-L23 (larger carcinoma) (Keawpradub *et al*., 1997). The plant also possess antimutagenic and immuno modulating properties.

Andrographis paniculata

Andrographis paniculata is also known as Kalmegh, belongs to family *Acanthaceae*. Andrographolide is major component in the leaves which is a bicyclic diterpenoid lactone (Kumar *et al.*, 2004). It exerts direct anticancer activity on cancer cells by cell cycle arrest at G0/G1 phase through induction of cell cycle inhibitory protein p27 and decreased expression of Cyclin dependent Kinase 4 (CDK4) (Rajagopal *et al*., 2003). Andrographolide has immunostimulatory activity by increasing the proliferation of lymphocytes and production of interleukin 2. It has indirect anticancer activity by increasing the production of tumor necrosis factor-α and CD marker expression, leads to increased cytotoxic activity of lymphocytes against cancer cells (Kumar *et al*., 2004). It also exhibits anti-typhoid, anti-hepatotoxic, anti-malarial, antiinflamatory and anti-fungal activities.

Azadirachta indica

Azadirachta indica, a member of the Meliaceae family, is known for its tremendous therapeutic and ethnomedicinal significance and that's why it has been designated as "the wonder tree" and "nature's drug store." Different reports are available for the use of almost all the parts, particularly leaves, bark, seed-oil and their purified products with more than 60 different types of ingredients including 35 biologically active principles viz., terpenoids and steroids are widely used for treatment and cure of various cancers. This plant with antitumorogenic activities has been recommended for the prevention, protection and suppression of tumors with immunomodulatory and apoptotic activities against various types of cancer with the modification of their molecular mechanisms and mode of action. The role of active principles in fore-stomach and skin papillomagenesis has been established with significant carcinogen detoxification in liver of swiss albino mice (Dasgupta *et al*., 2004; Paul *et al*., 2011).

***Betula* species**

Betulinic acid (a pentacyclin triterpene), isolated from *Zizyphus* species, (e.g. *mauritiana*, *rugosa* and *oenoplia*), belonging to family *Betulaceae*, is a common secondary metabolite of *Betula* species (Cichewitz and Kouzi, 2004), having selective cytotoxicity against melanoma cell lines of human origin (Pisha *et al*., 1995).

Camptotheca acuminate

Camptothecin, isolated from the Chinese ornamental tree *Camptotheca acuminate*, family Nyssaceae. It is also known as tree of joy in China and is a possible source of steroidal precursors for the production of cortisone. Topotecan and irinotecan are semi-synthetic derivatives of camptothecin and are used for the treatment of ovarian and small cell lung cancers and colorectal cancers, respectively (Bertino, 1997). But it was dropped because of severe bladder toxicity (Potmeisel and Pinedo, 1995).

Careya arborea

Careya arborea Roxb bark is commonly used in the treatment of tumors in ancient system of ethnomedical use and when methanolic extract of its bark were examined to evaluate the anticancer potentials against Dalton's lymphoma ascites (DLA)-induced ascitic and solid tumors in mice it produced significant reduction in percent increase in body weight with the increase of packed cell volume and viable tumor cell count. Moreover, histological observations of liver and kidney of affected and treated mice also indicated healing of tissue damage caused by tumor inoculation (Natesan *et al*., 2007).

Catharanthus roseus

Bioactive compounds are the vinca alkaloids include vinblastine, vincristine, vindesine and vinorelbine isolated from the Madagascar periwinkle, family Apocynaceae. Vinblastine and vincristine were first discovered during an investigation of the plant for potential oral hypoglycemic agents. They are used in acute leukemia, Hodgkin's disease, Wilms tumour, Swing's sarcoma, non-Hodgkin's lymphoma, rhabdomyosarcoma and neuroblastoma in case of humans and transmissible venereal tumor (TVT) in dogs. Vincristine has been used to treat many solid tumours like breast, colon, cervical, neck and head cancers in combination with other drugs. Vinfosiltine (S12363) is a new vinca alkaloid derivative and is 36 and 72 times more *in vitro* cytotoxic than vincristine and vinblastine, respectively (Adenis *et al*., 1995). Vinca alkaloids are involved in disruption of microtubules, anti mitotic, inhibition of protein and nucleic acid synthesis as well as calcium- calmodulin regulated cAMP phosphodiesterase activities, increase in glutathione oxidation and cAMP concentration, altered lipid metabolism and membrane lipid content (Tucker et al., 1977). *Vinca* alkaloid induces apoptosis via a pathway independent of cell

cycle arrest and along with their analogues is still crucial in the treatment of hematological malignancies and few solid tumour originating in lung and colon. It is also used for the treatment of blood pressure and diabetes mellitus.

Cephalotaxus harringtonia

Homoharringtonine, isolated from the Chinese tree *Cephalotaxus harringtonia* var. *drupacea,* belongs to family *Cephalotaxaceae* (Itokawa *et al*., 2005). A racemic mixture of harringtonine and homoha-rringtonine has been used successfully in China for the treatment of acute myelogenous leukemia and chronic myelogenous leukemia (Kantarjian *et al*., 1996; Cragg and Newman, 2005).

Clematis manhsrica

Clematis manshrica has obvious antitumor effects due to the presence of saponins. The Embelin derivatives such as 1, 4 – benzoquinone derivative 5-0 ethyl embelin (1) and 5-0 methyl embelin have therapeutic potential in decreasing the progression of cancer (Zhao *et al*., 2005).

Combretum caffrum

Combretastatins were isolated from the bark of the South African tree *Combretum caffrum,* belongs to family *Combretaceae* (Pettit *et al*., 1987). It acts as anti-angiogenic agents causing vascular shutdown in tumors and resulting in tumor necrosis. Combretastatin A-4 is the most cytotoxic phyto-molecule, active against colon, lung and leukemia cancers (Ohsumi *et al*., 1998).

Curcuma longa

The major active principles are curcumin sulphate and glucuronide. It induces apoptosis in various cancer cell types including colon, duodenum, fore-stomach, ovary and skin. Curcumin is the most chemopreventive agent, which allows suppression, retardation and invasion of carcinogenesis. It has antitumoral, anti-oxidant and anti-inflammatory principle capable of inducing apoptosis in numerous cellular systems (Duvoix *et al*., 2005). Curcumin can interfere the cell growth cycle of A549 cell and suppress cell growth (Zhang *et al*., 2004). It inhibits the growth of cancer by preventing production of harmful eicosanoid such as PGE-2. Curcumin suppresses mutagenic effect of various mutagens including cigarette smoke condensates, 7, 12-dimethylbenz (a) anthracene (DMBA) and benzopyrene. Curcumin decreases the levels of urinary mutagens. *Curcuma longa* inhibits production of nitrosamine and increases levels of glutathione that enhances natural antioxidant functions of the body. Curcumin is used to treat ulcerating oral cancer and squamous cell carcinoma of the skin. *Curcuma longa* also prevents malignant transformation of leukoplakia (Cheng *et al*., 2001). It also possesses anti-viral, anti-bacterial and anti-fungal activities.

Glycyrrhiza glabra

Glycyrrhiza glabra, also known as Licorice, belongs to family *Fabaceae*. The major constituents are glycyrrhizin, glabridin, glycyrrhetic acid, gycyrrhetinic acid and glycyrrhizic acid. Glycyrrhizin is the major component and possess anticarcinogenic and anti-inflammatory properties. It inhibits abnormal cell proliferation, tumor growth in breast, liver and skin cancer (Nishino *et al*., 1984; Shiota *et al.*, 1999). Licochalcone (LA) is a novel estrogenic flavanoid isolated from licorice root and has significant antitumor activity in various malignant human cell lines. LA induced moderate level of apoptosis but had more pronounced effect on cell cycle progression, arresting cells in G2 or M phase results in suppression of Cyclin B1 and cdc2. It also inhibits phosphorylation of Rb or S780 and decreases expression of transcription factor E2F concurrent with reduction of Cyclin D1 and down-regulation of CDKs 4 and 6, however increases the Cyclin E expression (Fu *et al*., 2004).

Indigofera aspalathoides

Indigofera aspalathoides (Papilionaceae), also commonly known as *Shivanar vembu,* as a whole plant is used in many routine activities as cooling, demulcent and odematous tumors along with certain cancerous affections (Kirtikar and Basu, 1975), whereas stem of the plant are used traditionally against cancer (The wealth of India, 2001). When ethanolic extract of *Indigofera aspalathoide*s (EEIA) were attempted against Dalton's ascitic lymphoma in Swiss albino mice and extracts protected effect in Dalton's ascitic lymphoma in mice (Christina *et al*., 2003). Moreover, in liver tumor of mice ethanol root extract of *Indigofera aspalathoides* reduced the impact of tumor inducer N-nitrosodiethylamine toxicity with further reduction of necrosis, suggesting chemoprotective effect against N-nitrosodiethylamine-induced hepatocellular carcinogenesis in swiss albino mice (Claimer *et al*., 2012; Garde, 2012).

Lawsonia inermis

Lawsonia inermis, commonly known as Mehndi, is also a well established medicinal plant and has been studied thoroughly for the alteration of phase-I and phase-II enzymes, antioxidant enzymes, glutathione content, lactate dehydrogenase and lipid peroxidation and the papillomatosis of fore stomach and liver of Swiss albino mice. It revealed chemopreventive response in the form of reduction in percentage of tumor bearing animals and tumor multiplicity (Dasgupta *et al*, 2003).

Morinda citrifolia

Morinda citrifolia L., from the coffee family, *Rubiaceae* is made up of around 80 species. It is commonly known as great morinda, Indian mulberry or noni in India and Nunaakal in Tamilnadu. In addition to the presence of bio-anticarcinogenic ingredients, the immune enhancement and nutritive supplementation properties of Noni helps to overcome maximum side effects and enhance efficacy of all chemotherapeutics against cancer cases including the breast cancer. *Morinda citrifolia* fruit juice has antitumour activity against Lewis Lung peritoneal Carcinomatosis (LLC) and cytotoxic activity against various cancer cell lines like neuroblastoma (LAN5) cell lines (36%), breast cancer (MCF7) cell lines (29%), human laryngeal carcinoma (Hep2) cells (13%), and colorectal cancer cells (HCT-116, SW480 and LoVo cells). Noni prevents DMBA-DNA adduct formation, Sarcoma 180 tumour and Ehrlich ascites tumor (EAC) (Wang and Su, 2001; Taşkin *et al*., 2009). It also prevents chemically induced tumorogenesis in the rat esophagus, peripheral T-cell non-Hodgkin's lymphoma, induced by N-Methyl N-Nitrosourea and Dibenzo [a,l] pyrene (DBP) along with breast cancer development and gastric cancer (Wong, 2004).

Ocimum sanctum

Ocimum sanctum, is called as *Tulsi* in India, belongs to family *Lamiaceae.* It is a tropical, much branched, annual herb. Biologically active compounds have been isolated from the leaves are apigenin, luteolin, ocimarin, ocimumosides A and B, ursolic acid, apigenin-7-*O*-β-D-glucuronic acid, luteolin-7-*O*-β-D-glucuronic acid 6″-methyl ester, luteolin-5-*O*-β-D-glucopyranoside and cerebrosides. Topical application of *Ocimum* extract significantly reduced the cumulative number of papillomas in DMBA-induced skin papillomagenesis in rats (Prashar *et al*., 1994). A significant 2-fold elevation of reduced glutathione content and increased glutathione S-transferase activity was also observed in the skin of extract treated animals. The plant extract prevents DMBA induced hamster buccal pouch carcinogenesis

Table 1. Plants/herbs, active principles and clinical uses against cancer

Sl. No.	Botanical name	Family	Anticancer compound	Anticancer activity against	References
1.	*Ammannia baccifera L.*	Lythraceae	Triterpenes, coumarins	Cervical cancer cell line (HeLa) and Dalton's ascitic lymphoma (DAL) induced solid and ascitic tumors	Loganayaki and Manian, 2012
2.	*Acacia catechu*	Leguminosae	Catechin	Cancer cell lines, COLO-205, HeLa and fibrosarcoma-HT 1080 cell lines	Nadumane and Nair, 2011
3.	*Acacia nilotica*	Mimosaceae	Terpenoids and Glycosides	Skin papillomagenesis and Dalton's ascitic lymphoma (DAL) induced solid and ascitic tumors	Meena *et al*., 2006; Sakthivel *et al*., 2012
4.	*Aegle marmelos*	Rutaceae	Lupeol	Breast cancer and primitive neuro-ectodermal tumours (PNET)	Lampronti *et al*., 2003
5.	*Aglaila sylvestre*	Meliaceae	Silvestrol	Lung and breast cancer cell lines	Hwang *et al.*, 2004
6.	*Aloe vera*	Aloaceae	Aloe-emodin and acemannan	Activates the immune cells against cancer.	Efferth *et al*., 2007; Chaudhary *et al.*, 2007
7.	*Alstonia scholaris*	Apocynaceae	Alstonine, echitamine chloride, villastonine, alkaloids like ditamine, echitamine and echitenines.	Human lung cancer	Keawpradub *et al*., 1997 ; Dung *et al*., 2001
8.	*Andrographis paniculata*	Acanthaceae	Andrographolide	Colon cancer	Rajagopal *et al*., 2003 ; Kumar *et al*., 2004
9.	*Azadirachta indica*	Meliaceae	Azadirachtin, Meliacin,	Murine carcinogenesis	Dasgupta *et al*., 2004; Paul *et al*., 2011
10.	*Betula* species	Betulaceae	Betulinic acid	Human melanoma cell lines	Pisha *et al*., 1995
11.	*Bleekeria vitensis*	Apocynaceae	Elliptinium, ellipticine	Breast cancer	Agarwal *et al*., 2011
12.	*Brucea antidysenterica*	Simaroubaceae	Bruceantin	Antileukemic activity	Gillin *et al*., 1982
13.	*Calotropis procera*	Asclepiadaceae	Cyclophosphamide	Myelosuppression, Mice Sarcoma 180 tumor	Choedon *et al.*, 2006; Oliveira *et al.*, 2007; Magalhaes *et al*., 2010
14.	*Camptotheca acuminate*	Nyssaceae	Camptothecin, Topotecan and irinotecan	Ovarian, small cell lung cancer and colo-rectal cancers	Bertino, 1997
15.	*Careya arborea Roxb*	Lecythidaceae	Piperine, Arborenin	Dalton's ascitic lymphoma (DAL) induced solid and ascitic tumors in mice	Natesan *et al*., 2007; Kumar *et al*., 2010
16.	*Catharanthus roseus*	Apocynaceae	Vinblastine, vincristine and vindesine	Leukemias, lymphomas, ad-vanced testicular cancer, breast cancer, lung cancer and Kaposi's sarcoma	Adenis *et al*., 1995
17.	*Centaurea schischkinii, Centaurea montana*	Asteraceae	Schischkinnin, Montamine	Human colon cancer cell lines	Shoeb *et al.*, 2006
18.c	*Centella asiatica*	Apiaceae	Vallarine, asiaticoside, sitosterol, tannin, oxyasiaticoside	Uterine cancer	Brinkhaus *et al*., 2000; Yoshida *et al*., 2005
19.	*Cephalotaxus harringtonia*	Cephalotaxaceae	Homoharringtonine	Acute myelogenous leukemia and chronic myelogenous leukemia	Kantarjian *et al*., 1996; Cragg and Newman, 2005
20.	*Cinnamomum cassia*	Lauraceae	Cinnamaldehyde, cinnamic acid	Human hepatoma Hep G2 cells	Ng and Wu, 2011
21.	*Chelidonium majus*	Papaveraceae	Benzophenanthridie derivatives	All types of cancers	Park *et al*., 2011
22.	*Combretum caffrum*	Combretaceae	Combretastatins (Combretastatin A-4)	Colon, lung and leukemia cancers	Ohsumi *et al*., 1998
23.	*Curcuma longa*	Zingiberaceae	Curcumin Sulphate	DMBA induced tumour, squamous cell carcinoma of the skin and the ulcerating oral cancer	Itokawa *et al*., 1982; Duvoix *et al.*, 2005
24.	*Dysoxylum binectariferum*	Meliaceae	Flavopiridol	Leukemia, lymphomas and solid tumors	Mohanakumara *et al*., 2010
25.	*Elepantopus elatus*	Asteraceae	Elephantopin	Breast cancer	Itharat and Ooraikul, 2007; Ahmad *et al*., 2009
26.	*Erythroxylum pervillei*	Erythroxylaceae	Pervilleine A	Multidrug resistant (MDR) oral epidermoid cancer cell line (KB-V1)	Mohanakumara *et al*., 2010
27.	*Ficus asperifolia*	Moraceae	Emodin, 3-geranyloxyemodin, 2-geranylemodin	A2780cis ovary cells	Tamokou *et al*., 2013
28.	*Glosiosa superba*	Liliaceae	Colchicine		The Plant List, 2010
29.	*Glycyrrhiza glabra*	Fabaceae	Glycyrrhizin	Breast, liver and skin cancer	Fu *et al.*, 2004
30.	*Heliotropium indicum*	Boraginaceae	Indicine-N-oxide	Acute leukemia and solid tumors	Fu *et al.*, 2002

31.	*Indigofera aspalathoides*	Papilionaceae	Indan, alkaloids and flavanoids	Dalton's ascitic lymphoma and Hepatocarcinogenesis in mice	Christina *et al*., 2003, Claimer *et al*., 2012
32.	*Lawsonia inermis*	Lythraceae	Dichloroallyl lawsone	Fore stomach, kidney and lung Papillomagenesis in mice	Dasgupta *et al*., 2003
33.	*Morinda citrifolia*	Rubiaceae	Scopoletin, rutin, Octoanoic acid, Nordamnacanthal, Morindone, Caproic acid and caprylic acid	Lewis Lung peritoneal Carcinomatosis (LLC), breast cancer, DMBA-DNA adduct formation, Sarcoma 180 tumour, Ehrlich ascites tumor and rat esophagus tumour	Wong, 2004
34.	*Moringa oleifera*	Moringaceae	4-(4'-*O*-acetyl-a-L-rhamnopyranosyloxy)benzyl isothiocyanate, niazimicin	Epstein-Barr virus (EBV) inhibition, Skin papillomagenesis in mice, Burkitt's lymphoma	Murakami *et al*., 1998; Bharali *et al*., 2003; Fahey J.W., 2005
35.	*Pentadesma butyracea*	Clusiaceae	cratoxylone, α-mangostin	four malignant cell lines: A2780 and A2780cis ovary cell cultures, A421 epidermal carcinoma and MW35 melanoma cell cultures	Lenta *et al*., 2011; Tamokou *et al*., 2013
36.P	*Phyllanthus niruri*	Euphorbiaceae	Phyllanthin, hypophyllantthi, lignansniranthin, nirtetralin, quercetin and phyltetralin.	Biliary and urinary tract cancer	Amir *et al.*, 2003 ; Naik and Juvekar, 2003
37.	*Podophyllum peltatum, Podophyllum emodi Podophyllum hexandrum*	Berberidaceae	Podophyllotoxin, Etoposide and Teniposide	Lymphomas, bronchial, lung and testicular cancers	Cragg *et al*., 1994; Giri and Narasu, 2000; Rahal *et al*., 2009
38.	*Psorospermum febrifugum*	Clusiaceae	Psorospermin, Emodin,	Leukemia, Hepatic and colon carcinoma, ovary, prostate, lung cancer	Kupcha *et al*., 1980; Wang *et al*., 2007; Li *et al*., 2009; Su *et al*., 2010; Ok *et al*., 2012; Suboj *et al*., 2012
39.	*Rosemarinus officinalis*	Lamiaceae	Caffeic and Rosmarinic acids,	Mouse skin tumorigenesis	Sancheti and Goyal, 2006a,b
40.	*Raphanus sativus*	Brassicaceae	Roscovitine	Ovarian cancer	Mezencev *et al*., 2009
41.	*Rubia cordifolia*	Rubiaceae	Rubiadin, purpurin and alizarin	Leukemia, ascitic carcinoma, large intestinal, lung tumors, melanoma and human cervical carcinoma JTC-26 cell line	Adwankar and Chitinis, 1982; Maker *et al*., 2005
42.	*Solanum dulcamara*	Solanaceae	β-solamarine	Hepatic and colonic carcinoma	Waggy, 2009
43.	*Tabebuia Species*	Bignoniaceae	Lapachol and β-lapachone	Leukaemia	Cragg and Newman, 2001
44.	*Taxus brevifolia*	Taxaceae	Paclitaxel (Taxol®) and docetaxel (Taxotere®)	Ovarian cancer, advanced breast cancer, small and non-small cell lung cancer	Cragg *et al*., 1993; Ghamande *et al*., 2003
45.	*Tinospora cordifolia*	Menispermaceae	tinosporin, berberine and gilenin	B16F-10 melanoma cells	Leyon and Kuttan, 2004; Aher and Wahi, 2010
46.	*Usnea*	Parmeliaceae	Usnic acid		Mayer *et al*., 2005; Hsu *et al*., 2005
47.	*Vismia laurentii*	Hypericaceae	Xanthones, anthraquinones and naphtoquinones	malignant cell lines: A2780 and A2780cis ovary cell cultures, A421 epidermal carcinoma and MW35 melanoma cell cultures	Kuete *et al*., 2011; Tamokou *et al*., 2013
48.	*Withania somnifera*	Solanaceae	Anahygrine, Beta-Sisterol, Chlorogenic acid, Cysteine and Withaferin	Inhibited DMBA induced skin papillomagenesis	Christina *et al*., 2004; Mathur *et al*., 2006 ; Mothana *et al*., 2007 ; Singh *et al*., 2009, 2010

(Karthikeyan *et al*., 1999). It has vast number of therapeutic applications such as in asthma, bronchitis, cardiopathy, catarrhal fever, gastropathy, genitourinary disorders, haemopathy, hepatopathy, hiccups, leucoderma, lumbago, otalgia, ophthalmia, ringworm, skin diseases and verminosis (Kumar *et al*., 2013).

Podophyllum species

Epipodophyllotoxin (isomer of podophyllotoxin) was isolated from the roots of *Podophyllum peltatum* and *Podophyllum emodi* (syn. *Podophyllum hexandrum)* family, *Berberidaceae*. Anticancer drug, etoposide and teniposide are semi-synthetic derivatives of epipodophyllotoxin and used in the treatment of lymphomas, bronchial and testicular cancers. It is a perennial herb and also known as Himalayan May apple, American mandrake or Indian May apple. It is used for treatment of skin cancers and warts. The plant contains anti-cancer lignans, podophyllin and berberine, which has antimiotic effect, interfere the cell division results in arrest of growth of cells. It is mainly used in the treatment of ovarian cancer. The rhizome of the plant contains a resin, known as Indian *Podophyllum* Resin, which is extracted for podophyllotoxin or podophyllin.

Podophyllotoxin acts as an inhibitor of microtubule assembly. It is used for treatment of testicular cancer, lung cancer, hepatoma and neuroblastoma (Chattopadhyay *et al*., 2004; Giri and Narasu, 2000). The entire plant, especially the root, is cytostatic purgative and cholagogue.

Rosemarinus officinalis

The study to explore the anti-tumor promoting activity of *Rosemarinus officinalis* on two-stage skin carcinogenesis revealed that the oral administration of Rosemary leaf extract during the period of pre, peri and post-initiational phases significantly decreased the tumor incidence at 50, 41.7, 58.3%, respectively, with the reduction of cumulative number of papillomas, tumor yield and tumor burden were also found to be reduced in *R. officinalis*-treated animals. Moreover, these results were found associated with significant alteration in liver lipid peroxidation and glutathione (GSH) levels (Sancheti and Goyal, 2006a; Sancheti and Goyal, 2006b).

Rubia cordifolia

The major chemical constituents of *Rubia cordifolia* are alizarin, munjistin, rubiadin, rubierythrinic acid, purpurin and pseudopurpurin. The extract of this plant contains cyclic hexapeptides, which has anti-cancer activity against leukemia, ascitic S180 carcinoma, large intestinal and lung tumors, melanoma and human cervical carcinoma JTC-26 cell line (Adwankar and Chitinis, 1982). It also possesses a significant antioxidant and immunomodulating properties.

Semecarpus anacardium

It is known as *Bhallatak* in India, belongs to family *Anacardiaceae*. The nuts of *S. anacardium* contain biflavonoids, phenolic compounds, bhilawanols, anacardic acid, cardol, catechol, anacardol and fixed oil (Premalatha and Sachdanandam, 1999). The nut extract of *S. anacardium* reduces the extracellular matrix (ECM) which normally present at an increased level in the early stage of invasion and responsible for the endothelial cell proliferation, development of vascular bed and invasion of tumour cells. It also caused the restoration of the factors associated with matrix and expression of MMP-1 to 3, TIMP-1 and TIMP-2 to normal values. The stabilization of the ECM with the reduced activity of proteases might inhibit the epithelial–endothelial interaction and tumour cell migration thus, inhibiting the adjacent invasion and tumour growth resulting in antineoplastic activity (Mathivadhani *et al*., 2007). It also possesses immunomodulatory and anti-inflammatory properties.

Taxus brevifolia

Paclitaxel (taxol®) was isolated from the bark of the Pacific Yew, *Taxus brevifolia, family Taxaceae*. It is a potent anticancer drug used to treat advanced breast cancer, cancer of lung and ovaries, and Kaposi's sarcoma (Sunwoo *et al.*, 2001; Luck and Roche 2002; Ghamande *et al.*, 2003). Paclitaxel has unique complimentary effect of its binding to polymerized tubulin, stabilizing it against disassembly and consequently inhibiting mitosis (Schiff and Horwitz, 1980). The remarkable stability of microtubules induced by paclitaxel is damaging to cells because of the perturbation in the dynamics of various microtubule dependent cytoplasmic structures that are required for cellular functions such as maintenance of cellular morphology, mitosis, neurite formation, secretion and locomotion. At lower concentration paclitaxel inhibits cells at G2 and M phase and inhibits cells in interphase at higher concentrations (Fan, 1999). Infusions, decoctions and poultices of leaves and bark of the tree are used for treating stomach ache, lung problem, pain and wound.

Terminalia arjuna

The major chemical constituents are glycoside, arjunetin and flavones arjunone, cerasidin, friedlin, methyl oleanolate, sitosterol, gallic, ellagic and arjunic acids arjunetosides I-IV. It also contains tannins and triterpenes, which has antigenotoxic or antimutagenic effects. The flavone Luteolin inhibits various cancer cell lines (Pettit *et al.*, 1996). Casuarinin was isolated from the Bark of *T.arjuna* inhibited breast cancer cell growth. It induces apoptosis and cell cycle arrest in human breast adenocarcinoma MCF-7 Cells (Kuo *et al*., 2005). In Ayurveda, it is used as alexiteric, styptic, expectorant, aphrodisiac, anthelmintic diuretic, tonic and useful in ulcers, fractures, heart diseases, urinary discharges, biliousness, asthma, anaemia, leucoderma, excessive prespiration etc.

Tinospora cordifolia

Tinospora cordifolia is called *Guduci* in Sanskrit, meaning the one which protects the body. It is also called as *amrta* or nectar and belongs to family *Menispermaceae*. The active principles are glycoside *viz.* giloin, alkaloids, and a non-glycoside, gilenin, gilosterol and alkakoid tinosporin, tinosporic acid, tinosporol, berberine, tinosporidine and sitosterol and a new furanoid diterpene, tinosporide (Singh *et al*., 2003). Polysaccharide fraction of *T. cordifolia* was very effective in reducing the metastatic potential and antiangiogenic activity in B16F-10 melanoma cells. It has positive effect on leucocytes suggests its use as adjuvant in cancer therapy. It activates macrophage and leads to increase in colony forming units, results in leucocytosis and enhancement in neutrophil function (Leyon and Kuttan, 2004). It has immunostimulatory properties. It is also used for treatment of anaemia, cardiac debility, diabetes, raktapitta, sexual debility and spleenic disorders (Singh *et al*., 2003).

Withania somnifera

Withania somnifera is known as *Ashwagandha* or Indian ginseng in India, belongs to family *Solanaceae*. The active principles include anaferine alkaloid, anahygrine, chlorogenic acid (in leaf only), beta-Sisterol, fruit cysteine, iron, scopoletin, somniferinine and somniferiene, tropanol, withananine, withanine and withanolides A-Y (Steroidal lactones). The principle constituents of its root, withanolides possess immuno- modulatory activity, Withaferin A and Withanolide D inhibits growth of cancer (Mathur *et al.*, 2006). The extract of this plant inhibited benzo (a) pyrene-induced forestomach papillomagenesis, showing up to 60 and 92% inhibition in tumor incidence and multiplicity, respectively. It also inhibits DMBA-induced skin papillomagenesis, showing up to 45 and 71% inhibition in tumor incidence and multiplicity, respectively (Padmavathi *et al*., 2005). The extract of this plant acts on the Hypothalamic Pituitary Adrenal (HPA) axis and the neuroendocrine system.

Zingiber officinalis

The rhizome *Zingiber officinalis*, is a widely used species of the ginger family and is called "The Great Medicament" in Ayurveda. The pungent Vallinoids, 6-gingerol and 6-paradol along with shogaols and zingerone are attributed to the anticancer properties (Shukla and Singh, 2007).

Miscelleneous herbs effective against cancer

Asiasarum heterotropoides var. mandshuricum F. Maekawa (A. *radix*) can inhibit the growth of the HCT-116 cells through induction of G2/M cell cycle arrest and apoptosis (Oh *et al*., 2013). *Viscum cruciatum* Sieb. Ganoderic Acids (GAs) from *Ganoderma lucidum* mushroom have been used for prevention and control of cancer and other diseases since centuries as it possesses both anti-inflammatory and anti-cancer activities (Radwan *et al*., 2011; Assaf *et al*., 2013). Berberine (BBR), obtained from Chinese herbal medicine induces apoptosis in cancer cells by down regulating the death-domain-associated protein (DAXX) expression at the transcriptional level (Li *et al*., 2013). Jiedu Xiaozheng Yin (JXY), a polyherbal formula of traditional Chinese medicine inhibit the growth of tumors by suppressing the expression of vascular endothelial growth factor A (VEGF-A) and vascular endothelial growth factor receptor 2 (VEGFR-2) (Cao *et al*., 2013). In traditional Ayurvedic medicine plant like *Asparagus raceemosus*, which is a rich source of phytoestrogens, has been used. The presence of glutathione and cell growth factor like histone at a greater concentration has made this plant valuable to treat various types of cancers (Diwanay *et al*., 2004; Bopana and Saxena, 2007). Various botanical plants found in different parts of the Indian subcontinent are found to be effective against tumours of brain and uterus; abdomen and glandular organs along with certain plants effective against throat and breast cancer are used widely in different parts of India. Use of different parts of *Acrorus calamus* L.(Sweet flag); *Anamirta cocculus* (Levant berries); *Aphanamixis polystachya* (Pitraj-daru); *Bauhinia racemosa* (Lamk Common mountain); *Borassus flabellifer* (Palmyer palm); *Derris scandens* (Derris root); *Dicanthium pertusum* (Begi-gash: tribal name); *Hemidesmus indicus* (Indian Sarsaparilla); *Holarrhena pubescens* (Conessi bark); *Nerium indicum* (Greater Indian oleander) and *Viscum orientale* (Mistletoe) require special mention in this regard (Posey, 1999; Wargovich *et al*., 2001; Wynn, 2001; Carrio *et al*., 2012; Poojari *et al*., 2012).

Conclusion and Future Perspectives

Cancer is the leading cause of death in India as well as the third world countries. As there is an enormous increase in the population day by day, the alternative therapy in the market is gaining its importance. Sophisticated therapeutic strategies in modern medicine, though effective in controlling and management of cancer that infect humanity, do not reach all sections of human populations in all corners of the world due to the problems of affordability and as a consequence, large number of human populations still depend up on plant based traditional alternative systems of medicine to combat debilitating diseases and cancers. Many compounds isolated from herbal extracts are used to treat various diseases in modern medicine because of their potent biological activities. Owing to the awareness about the side effects and toxicity of the synthetic drugs used in modern therapy, there is an increasing interest in herbal drugs or traditional medicine in recent times. Apart from the economic benefits, they can also be ideally recommended to the rural people for effective treatment of various types of cancers. They do not cause toxicity, so used to combat cancer, and maintain the health and vitality of individual. More than 270,000 higher plants exist in the world, but only a limited portion has been explored phytochemically, thereby generating only a product for cancer treatment. However, an array of herbs and herbal products having promising anticancer properties exist, therefore, it is anticipated that plants can provide potential bioactive compounds for the development of new therapies to combat cancer diseases. But their efficacy in humans and animals need to be evaluated fully. The discovery of several benefits of herbs as remedial for cancer is still on the way. Proper standardization methods for good agricultural practice, production of raw materials, collection of plant material, good post harvest handling and good manufacturing practices have to be followed for herbal drugs. Isolation and purification of biologically active components from the bulk extract, to understand the basic mechanisms of the drug action are warranted. Rigorous safety and quality evaluation and comparative clinical studies using modern techniques are essential to validate the efficacy of several of the herbal traditional drugs but insufficient funds may often make the whole process slow. One however must take into consideration the fact that herbs may create a serious difference to the health of man and animals and clear and informed advice in this regard is the need of the hour.

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