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Herbs to support cancer care: Challenges and opportunities

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Abstract

Application of plant and plant derived compounds in management and treatment of cancer dates back to early 19th century. More than 60% of the drugs clinically used for treatment or management of cancer today are either modifications or derivatives of natural products. Natural molecules have shown success due to their safety to normal or noncancerous cells along with ability to trigger multiple pathways for targeting cancer cells. These natural molecules were used in modified form to either achieve optimum pharmacokinetic parameters or for optimum activity. Conversely, many of the herbs (whole herbs, parts of herbs, crude or semi processed extracts) have been explored benefit in both treatment and management of tumors of different origin and molecular character. Most of these studies are well documented using in vitro, cell lines or animal models and very few reports are available reading clinical studies. The available clinical studies are either observational or retrospective analysis of very few cases. In this article, we are discussing the advantages of herbaceuticals (Herbs and its preparations) for cancer care and challenges in subjecting these products for clinical studies. Information will also be provided regarding existing opportunity and challenges to undertake scientific clinical investigations of herbs for supporting cancer care.

Keywords: Cancer care; Clinical studies; Herbaceuticals; Integrated medicine; Traditional medicine

Abbreviations: VRLB: Vinorelbine; VDS: Vindesine: WHO: World Health Organization; EFCAM: European Federation for Complementary and Alternate Medicine

History of Plant Based Treatment of Cancer

Natural products from plants serve as most promising source of potential drug leads [1]. Estimation of the world's diversity for potential biological aspect is less than 10, a myriad of applicable natural lead compounds await discovery [2]. In addition to most popular Indian system of medicine Ayurveda (herbs were major medicines uses), which is 5000 year old (Approx. 3000 BC), there are several reports from other parts of the world. The ancient records of natural products from Mesopotamia (2600 B.C.) were delineated on clay tablets in cuneiform which documented oils from *Cupressus sempervirens* (Cypress) and *Commiphora* species (Myrrh) which are being used till date to treat coughs, colds and inflammation. An Egyptian pharmaceutical record, The Ebers Papyrus (2900 B.C.) has documented over 700 plant-based drugs ranging from gargles, pills, infusions, to ointments. Arabs were the first people to own private pharmacies (8th century) with Avicenna, a Persian pharmacist, physician, philosopher and poet, volunteering much to pharmacy and medicine through works such as the *Canon Medicinae* [3]. This speaks about application of herbs as medicine globally from ancient period. Application of natural products as medicines has been portrayed throughout history in the form of traditional medicines, remedies, potions and oils. The utility and knowledge of natural product from medicinal plants results from the experimentation by man for hundreds of centuries through palatability trials or the occurrence of untimely deaths, quest for available herbs for the treatment of diseases [4].

Plants have evolved and adapted over millions of years to withstand pathogens, insects, fungi and climate and seasons to produce unique, structurally diverse secondary metabolites [5]. These molecules have shown ability to treat several pathological conditions in human, which includes cancer and inflammation. According to World Health Organization (WHO), about 80% of people still rely on plant-based components as traditional medicines for primary health care [6]. The health benefits rendered from traditional medicine from plants has promoted further studies and investigations of medicinal plants as potential therapeutic medicines and has also paved way to the isolation of many natural products which are been well established pharmaceuticals used globally.

Application of Plant Based Molecules/ Derivatives in Treatment of Cancer

Paclitaxel (Taxol®), isolated from the bark of *Taxus brevifolia* (Pacific Yew) is a commonly used well known drug for breast

cancer [3]. Ingenol 3-O-angelate a derivative of the polyhydroxy diterpenoid ingenol isolated from the sap of Euphorbia peplus, is a potential chemotherapeutic agent for skin cancer and is clinical development by Peplin Biotech for the topical treatment of certain skin cancers [7-8]. Combretastatin A-4 phosphate, a stilbene derivative from the South African Bush Willow, *Combretum caffrum* acts as an anti-angiogenic agent causing vascular shutdowns in tumors (necrosis) and has compleated Phase II clinical trials [9].

As mentioned earlier, plants play a major role as effective anti- cancer agents, and it is reported that about 60% of anti-cancer agents used currently are derived from natural sources, including plants, marine organisms and micro-organisms [3,10]. Vinca alkaloids, vinblastine and vincristine, and the isolation of the cytotoxic podophyllotoxins were the earliest notable discoveries of anti-cancer agents, dated to 1950's. It is said that any of the new plant based anticancer agents are yet to reach the general use, as a number of them ate in preclinical development [11].

Vinblastine and vincristine isolated from the Madagascar periwinkle, *Catharanthus roseus* G. Don. (Apocynaceae), were the first few plant derived agents to enter clinical use and they were used for primarily treating diabetes [12]. The study of these agents as potential oral hypoglycemic agents, it was observed that these extracts reduced the count of white blood cells and caused the depression of bone marrow in mice, and subsequently they were found to be active against lymphocytic leukemia in mice. This paved a way for the isolation of these compounds. Recently these compounds are prepared in semisynthetic analogs called vinorelbine (VRLB) and vindesine (VDS). These agents are used in combination with other cancer chemotherapeutic drugs for the treatment of a range of cancers, including leukemias, lymphomas, advanced testicular cancer, breast and lung cancers, and Kaposi's sarcoma. Etoposide (VM 26) and teniposide (VP 16-213 are two clinically active compounds which are semi-synthetic derivatives of epipodophyllotoxin (an isomer of podophyllotoxin), which are used for the treatment of cancer [13]. The *Podophyllum* species of Indian subcontinent regions have been used since ancient days for the treatment of skin cancer and warts. The species includes *Podophyllum peltatum* Linnaeus (commonly known as the American mandrake or Mayapple), and *Podophyllum emodii* Wallich. Etoposide and teniposide are two other efficient agents that were discovered for the treatment of lymphomas and bronchial and testicular cancers. The exploration of taxanes was a major stepping stone towards the treatment of cancer [14]. Paclitaxel (taxol®) was isolated initially from the bark the Pacific Yew, *Taxus brevifolia* Nutt. (Taxaceae). The use of various parts of Taxus brevifolia and other *Taxus* species (e.g., *Taxus Canadensis* Marshall, *Taxus baccata* L.) by Native American tribes for the treatment of some cancer and non-cancerous conditions has been reported, [15]. Baccatins, one of the several key precursors of paclitaxel occurs in the leaves of various *Taxus* species. Its native and semi-synthetic form of baccatins along with docetaxel (Taxotere®), paclitaxel analogs, stands as a major class of anticancer drugs. Paclitaxel remains as one of the potential agents in the treatment of breast, ovarian, and non-small cell lung cancer, while docetaxel is primarily used in the treatment of breast cancer and non-small cell lung cancer.

Another important addition to the anti-cancer drug armamentarium is the class of clinically active agents derived from. Camptothecin (as its sodium salt) was advanced to clinical trials by the NCI in the 1970s, but was dropped later because of severe bladder toxicity, but extensive research led to the development of more effective derivatives, Topotecan and Irinotecan (CPT-11; Camptosar). Topotecan, a derivative of camptothecin, isolated from the Chinese ornamental tree, *Camptotheca acuminata* Decne (Nyssaceae) [16] is used for the treatment of ovarian and small cell lung cancers. Another derivative of camptothecin, Irinotecan is used for the treatment of colorectal cancers.

Application of plant phytochemicals in cancer

A whole range of chemical compounds have been developed for the treatment of cancer. They impose limitations due to their inability to solely targeting the cancer cells [17]. Naturally derived compounds from plants stands as an absolute alternative source to overcome these issues.

The secondary metabolites synthesized in plants such as polyphenols, flavonoids and brassinosteroids have been extensively extracted and studied for their potential use as anticancer agents. They possess a range of anticancer activities which include; antioxidant activity; inhibition of cancer cell growth; induction of apoptosis; target specificity; cancer cell cytotoxicity [18,19]. These natural compounds are available readily from the natural environment and are relatively non-toxic to human cells. Nanotechnology has been a development in administration of anticancer compounds and therapies in the form of nanoparticles. The method allows the controlled and sustained release of the active agents and reduces the severe side effects. Treatment and prevention of cancer using plant based compounds is attributed to their safety, low cost, and oral bioavailability. Cancer conventional therapies like chemotherapy and radiotherapy can induce side effects such as myelosuppression and neurological, cardiac, pulmonary, and renal toxicity, which pose serious harm to the quality of life [20]. This necessitates the need of more potent and less toxic anticancer drugs.

Limitations of plants in cancer care

The demand for plant-derived drugs is increasing the pressure on potential medicinal plants and risking their biodiversity [21]. In spite of huge demand for natural and alternate sources of chemotherapeutic and chemo preventive molecules or formulation, we are not able to identify most efficient formulation due several limitation. This includes, Lack of scientific evidence on benefit of herbs and herbaceuticals

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in cancer care, which includes toxicity profile, molecular mechanism, information about active principles. Unlike synthetic drug molecules, there are no guidelines for clinical investigations of plant based or dietary ingredients. As working principles of traditional medicine and modern medicine are different, it is difficult to follow the evaluation model for clinical investigations [22-27]. There are several efforts to address this issues globally through National Institute of Health (USA), Department of AYUSH (India), Complementary and integrative medicine (Australia), European federation for complementary and alternate medicine (EFCAM), Complementary and Natural Healthcare council (UK), traditional Chinese medicine (China), traditional medicine (Republic of Korea), traditional system (Africa). These bodies are focusing on application of alternative (where herb based is the major components) medicine for selected health conditions for which there is no definite remedy in modern medicine. As a part of such health condition, cancer is most common disease addressed by complementary/ alternate system of medicine for both treatment and management. In many countries, there are no guidelines, licensing authority for use and practice of alternate or traditional system of medicine [28-35]. However, the same can be used by qualified health care practitioners who have good knowledge of its safety and efficacy.

In order to overcome these limitations, it may be a good idea to have an international forum or guidelines on the use of plant based or natural medicines for health care and promotion. Such a forum should encourage researchers and medicine practitioners across the discipline to join hands to fight against cancer. They should encourage and support joint efforts of researchers from Agriculture, Modern medicine, Chemistry, Botany, Pharmacology, Alternate system of medicine, Pharmaceutical sciences and Molecular biology to address the complexity of issue in integrated manner. Additionally, specific guidelines for undertaking research on clinical utility of herbs and natural products should be included to existing polity or a separate guidance to be made [36,37]. Chemical, Taxonomical profiling should be done to each of the herb used and optimized protocol to be established for cultivation, collection and processing of each plant material used. This can specifically help to address the issue related to variation in active ingredients in different plants (caused due to seasonal and time of harvest or collection of plant material), which is a major concern in herbaceuticals [38-44].

Summary

It is well established fact that most of the successful clinical chemotherapeutic drugs have history natural origin specifically from herbs. With lot of challenges posed by signs and symptoms of cancer due to genetic and molecular complexity, we are not successful in addressing the same effectively for last 5 decades. The only ray of hope during this period was findings on several herbs and its constituents, which have shown positive repose towards inhibiting tumor and associated pathological conditions. We have discussed these results in our previous article (Swaroop et al., 2014). These findings are either in preclinical and clinical studies with very small size. There are several evidences of clinical success from alternate and traditional medicine practitioners which is either not documented or poorly documented. Scientific clinical investigations with integrated approach among traditional, integrated and modern medicine practitioners may provide best solutions. Along with this some of the legal and statutory bodies governing different system of medicine should come up with regulations that can support such integrative approach for better outcome. Asia and Africa are known for rich and diverse source of herbs with medicinal value, integration of researchers from this continent with other advanced scientist of natural products, combinatorial chemistry and advanced molecular medicine may provide better outcome towards search of best medicine for cancer care (Table 1 & 2) [22-44].

Table 1: Herbs known for prevention of cancer incidences based on in vitro, in vivo studies (Adopted from Raina et al., 2014).

Herb/ Plant name	Active Phytochemicals	Major activity/ mode of action	References
Actaea racemosa L.	Cycloartenol, Actein	Inhibits proliferation of human breast cancer cells and human liver cancer cells (HepG2)	22
Allium sativum L.	Allylmercaptocysteine and thioallyl compounds	Antiproliferative effect of thioallyl against breast and prostate cell lines Inhibition of IL-6	23
Andrographis paniculata Wall. ex Nees	Deoxyandrographolide, andrographolide	expression, suppresses IL-6-mediated signals, and induces cell apoptosis by the activation of apoptosis-related proteins/ MAPKs, cytotoxic agent in the case of liver cancer	24
Ardisia crenata Roxb	Alkenylphenol, Ardisiacrispins A and B	Inhibits the uncontrolled proliferation by inducing proapoptotic and microtubule disruptive activities.	25
Boswellia serrata Roxb.	Acetyl-11-keto-β-boswellic acid (AKBA)	Inhibition of multiple steps of VEGF-induced cell proliferation, migration, invasion, and tube formation.	26
Catharanthus roseus (L.) G.Don	Vinblastine and Vincristine	Curative effects against human neoplasms. Therapy for lymphosarcoma, choriocarcinoma, neuroblastoma, and carcinoma of the breasts, lungs and other organs in acute and chronic leukemia..	27

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Centella asiatica L.	Glycoside asiaticoside, Asiatic, madecassic acid.	Decrease the viability of HepG2 cells due to increased expression of a tumor-suppressor p53 gene mediated by increased levels of intracellular calcium	28
Curcuma longa L.	Curcumin	Antitumor potential via suppression of transcription factor, NF-κB, AP-1, and STAT-3. Also repress pro-inflammatory pathways of COX-2 and iNOS	29
Fagara zanthoxyloides L.	Benzophenanthridine alkaloid fagaronine	Antitumor activity against murine leukemic cell lines in vivo. Fagaronine inhibits the DNA replication of rapidly growing cancer cells by inhibiting DNA and RNA polymerase activities and protein synthesis	30
Glycyrrhiza glabra L.	Isoliquiritigenin (2′,4′,4-trihydroxychalcone),	Induction of phase II enzymes such as quinone reductase 1, increased expression of glutathione peroxidase 5, and downregulation of several cytochrome P450 genes	31
Glycyrrhiza glabra L.	Terpenoids, alkaloids, and glycosides Indirubin	Potent inhibitor of cyclin-dependent kinases. Inhibits the proliferation Cells by arresting the cells in the G2/M phase of the cell cycle	32
Mangifera indica L.	Triterpene called lupeol	Induce apoptosis in human epidermoid carcinoma A431 cells. Induction of apoptosis in association with the caspase-dependent mitochondrial cell death pathway. It also inhibits the Akt/PKB signaling pathway by inhibition of Bad (Ser136) phosphorylation.	33
Morinda citrifolia L.	Glycosides, 6-O-(β-D-glucopyranosyl)-1-Ooctanoyl-β-D-glucopyranose and asperulosidic acid,	Inhibiting TPA- or EGF-promoted cell transformation as well as related AP-1 activity in the mouse epidermal JB6 cell line (Liu et al., 2001). Increased	34
Nigella sativa L.	Thymoquinone,	Supression of NF-κB, Akt activation, and extracellular signal-regulated kinase signaling pathways; it also inhibits tumor angiogenesis	29
Panax ginseng C.A.Mey.	Saponins, Ginsenosides	Antiproliferation, antiinvasion, and antiangiogenesis properties.	35
Plumbago zeylanica L.	Plumbagin, quinoid	Inhibitory against molecular targets like protein kinase C epsilon (a PCa proliferative marker), STAT-3, AKT, and PI-3K result in the inhibition of growth and invasion of PCa.	36
36Rhinacanthus nasutus (L.) Kurz	Rhinacanthins M, N, and Q and related	The partial arrest of cells at the G2/M has been observed and leads to apoptosis	37
Scutellaria baicalensis Georgi	Baicalein, Wogonin, Wogonoside	Inhibition of 12-lipoxygenase activity	38
Solanum incanum L.	Solamargine	Potential as an anticancer agent for tumor necrosis factors and Bcl-2-related resistance of human lung cancer cells	39
Vismia laurentii De Wild.	Xanthone V1	Apoptosis induction, and caspase-3/7 activity in the CCRF-CEM cell line and show evidence for its anticancer potential as a cytotoxic agent.	40

Table 2: Native and traditional herbs undergone clinical studies and used in traditional practice of medicine.

Plant/ herb	Part or formulation	Cancer and study design	Major findings	References
Turmeric	Powder of rhizomes of *Curcuma* Sp.,	Colon cancer Phase-I	3.6 g showed significant decreases in PGE2	41
Morinda citrifolia (Noni)	Fruit Juice		Immune boosting	42
Astragalus species	Whole herb along with other drugs	Non-small lung cancer Meta-Analysis of Randomized Trials	Astragalus-based Chinese herbal medicine may increase effectiveness of platinum-based chemotherapy when combined with chemotherapy.	43
Kampo Medicines-Traditional Japanese medicines	Consist of 5-12 herbs	Hepatic cancer Phase III randomized trial	Up to 40% reduction in death	44
β-Gluean Mushroom Extracts	Polysaeeharide K (PSK)	Colorectal Randomized trail	Increased disease free status and survival	44

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Green tea	Tea	Case control study Colon and rectal cancer	Reduced the overall burden	44
Mistletoe	Refers to Viscum album *species*	Randomized trail Head and neck cancer	Better outcome	44
Essiac	Consist of Burdoek, Turkey rhubarb, Sorrel, Slippery elm	Observational studies Colon and other cancers	Overall survival and quality of life	44

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