WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.045
Volume 3, Issue 6, 305-319. Review Article ISSN 2277 – 7105

# ETHNOMEDICINE IN CANCER THERAPY: A REVIEW

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Article Received on
01 June 2014,

Revised on 26 June 2014,
Accepted on 21 July 2014

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## INTRODUCTION

Ethnomedicine is the study of the traditional medicine (indigenous or folk medicine) practiced by various ethnic groups, and by indigenous people. Hence the word ethnomedicine can be used as a synonym for traditional medicine. These Traditional knowledge systems are developed over generations within various societies before the era of modern medicine. At present, majority of the people in developing countries rely on traditional medicine for their primary healthcare, and about 85% of traditional medicines involve the use of plant extract. [1, 2] In all countries of the world, there exist different forms of traditional knowledge related to the health of human beings and animals. The definition of traditional medicine given by the World Health Organization (WHO), may be summarized as 'the sum total of all the knowledge and practices, whether explicable or not, used in the diagnosis, prevention and elimination of physical, mental or social imbalance and relying exclusively on practical experience and observation handed down from generation to generation, whether verbally or in writing'. [3]

The WHO has also recognized the important role of traditional medicine in developing countries. WHO accepts that traditional systems will continue to play an important part in providing services to very large numbers of people, particularly in rural areas. Treatment according to traditional medical systems are often cheaper due to the local availability and accessibility of herbs and other traditional medicines. Indigenous practitioners in India treat the patients according to the principles of three ancient systems of Indian medicine; the Ayurvedic, the Siddha medicine of Sourth India, and the Unani or Graeco-Arabic medicine.[4] Ethnopharmacology is defined as the interdisciplinary scientific exploration of biologically active agents traditionally employed or observed by man. The ethnopharmacologic approach

is based on botany, chemistry and pharmacology which include field observations, and descriptions of the use and effects of traditional remedies, botanical identification of the plant species and phytochemical and pharmacological studies for its validation. The ultimate objectives of ethnopharmacology are to rescue and document important cultural heritage before it is being lost, and to investigate and evaluate the agents employed for the search of newer effective therapeutic molecules.[5] Thus ethnomedicine/ ethnopharmacology aim on health care based on natural resources.

With the emerging interest of the world in adopting and understanding traditional systems, and in exploiting their potential from different healthcare perspectives, the Government of India has initiated several attempts to explore these systems for their potential. The Ministry of Health and Family Welfare, Government of India, has undertaken various initiatives for the development and preservation of these aspects of cultural heritage. The Department of AYUSH (Ayurveda, Yoga, Siddha, Unani and Homeopathy) regulates education and research in these systems. The National Medicinal Plant Board [NMPB], which deals with conservation and research issues in botanicals, is working to address issues in those areas.[5]

**Understanding Cancer**

Cancer is a generic term for a large group of diseases that can affect any part of the body. Other terms used are malignant tumours or neoplasms. Cancer is characterized by rapid and uncontrolled formation of abnormal cells, which may mass together to form a growth or tumor, or proliferate throughout the body, initiating abnormal growth at various other sites. If the process is not arrested, it may progress until it causes the death of the organism. A Cancer cell also has the character of immortality even in vitro whereas normal cells stop dividing after 50-70 generations and undergoes programmed cell death (apoptosis). Metastasis is considered as the most lethal aspect of carcinogenesis.[6]

Cancers figure among the leading causes of death worldwide, accounting for around 8 million deaths per year. Lung, liver, stomach, colorectal and breast cancers cause the most cancer deaths each year. Modern medicine attributes most cases of cancer to changes in DNA that reduce or eliminate the normal controls over cellular growth, maturation, and programmed cell death. These changes are more likely to occur in people with certain genetic backgrounds such as familial prevalence of certain cancers, and in persons infected by chronic viruses (e.g., viral hepatitis may lead to liver cancer; HIV may lead to lymphoma). The ultimate cause, regardless of genetic predisposity or viruses that may influence the risk of the cancer,

is often exposure to carcinogenic chemicals and/or to radiation coupled with a failure of the immune system to eliminate the cancer cells at an early stage in their multiplication .[7] Tobacco use, alcohol use, unhealthy diet and physical inactivity are regarded as the main cancer risk factors worldwide.

The main treatment modalities for cancer include radiotherapy, surgery and chemotherapy (cancer chemotherapeutic agents). A successful anticancer drug should kill or incapacitate cancer cells without causing excessive damage to normal cells. This ideal is difficult, or perhaps impossible, to attain and is the reason why cancer patients frequently suffer unpleasant side effects while under-going the treatment.[8]

**HERBS AS SOURCE OF ANTICANCER AGENTS**

Plants have played an important role as a source of effective anti-cancer agents, and it is significant that over 60% of currently used anti-cancer agents are derived in one way or another from natural sources, including plants, marine organisms and micro-organisms. [9, 10]
The search for anti-cancer agents from plant sources started in earnest in the 1950s with the discovery and development of the vinca alkaloids, vinblastine and vincristine, and the isolation of the cytotoxic podophyllotoxins. United States National Cancer Institute (NCI) initiated 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 [11], including the taxanes and camptothecins, and are developed as clinically active agents over a span of some 30 years, from the early 1960s to the 1990s. So far, pharmaceutical companies have screened more than 25,000 plants for isolating and developing anti-cancer drugs and a number of agents are in preclinical development. [12]

The resistance developed by many cancer patients to treatment with standard anti-cancer agents due to its repeated exposure is a serious problem encountered in cancer chemotherapy. The resistant cancer cell population may subsequently show broad cross-resistance to other anti-cancer agents even though it has never been exposed those agents, which is called as multidrug resistance (MDR). MDR may be related to the presence of an MDR1gene encoding a protein (Pgp; P-glycoprotein) which effectively pumps the drugs out of the cell, thereby preventing their anti-tumor actions. Several synthetic compounds which reverse this effect *in vitro* in cell line studies (called MDR inhibitors) have been discovered, but their effectiveness *in vivo* is found to be disappointing in many cases, so there is a continuing search for more

effective MDR inhibitors. In contrast, certain compounds isolated from plants like 'pervilleines' isolated from the Madagascar plant, *Erythroxylum pervillei* Baillon, have shown promising MDR activity both *in vitro* and *in vivo*, and pervilleine A is currently in preclinical development. [13]

**Plant-Derived Anti-Cancer Agents In Clinical Use**

**Vinca alkaloids**

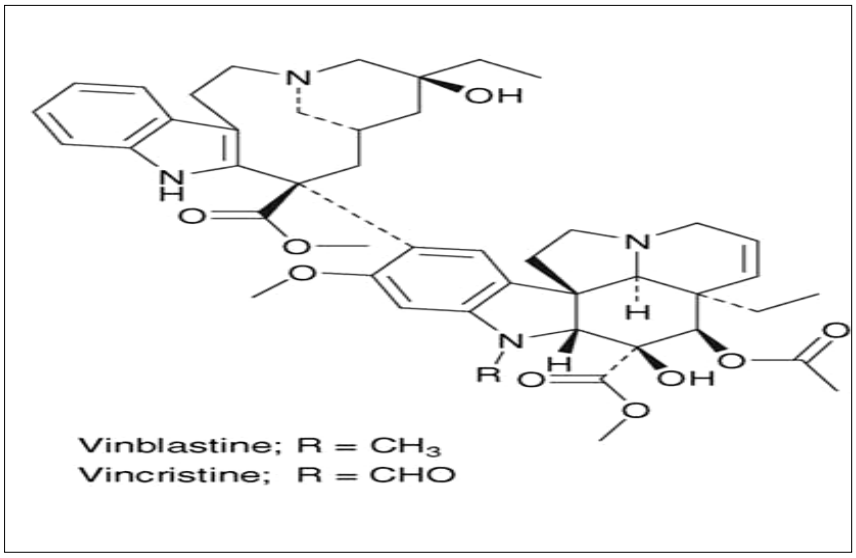


**Figure 1: chemical structure of vinca alkaloids**

Vinblastine (VLB) and vincristine (VCR), isolated from the Madagascar periwinkle, *Catharanthus roseus* which was used traditionally for the treatment of diabetes, [14] are the first plant derived anticancer drugs came into clinical use. While under investigation as a source of potential oral hypoglycemic agents, it was noted that extracts of *Catharanthus roseus* reduced white blood cell counts and caused bone marrow depression in rats, and subsequently they were found to be active against lymphocytic leukemia in mice. This led to the isolation of VLB and VCR as the active agents. More recent semisynthetic analogs 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, including leukemias, lymphomas, advanced testicular cancer, breast and lung cancers, and Kaposi's sarcoma.

**Podophyllotoxin**

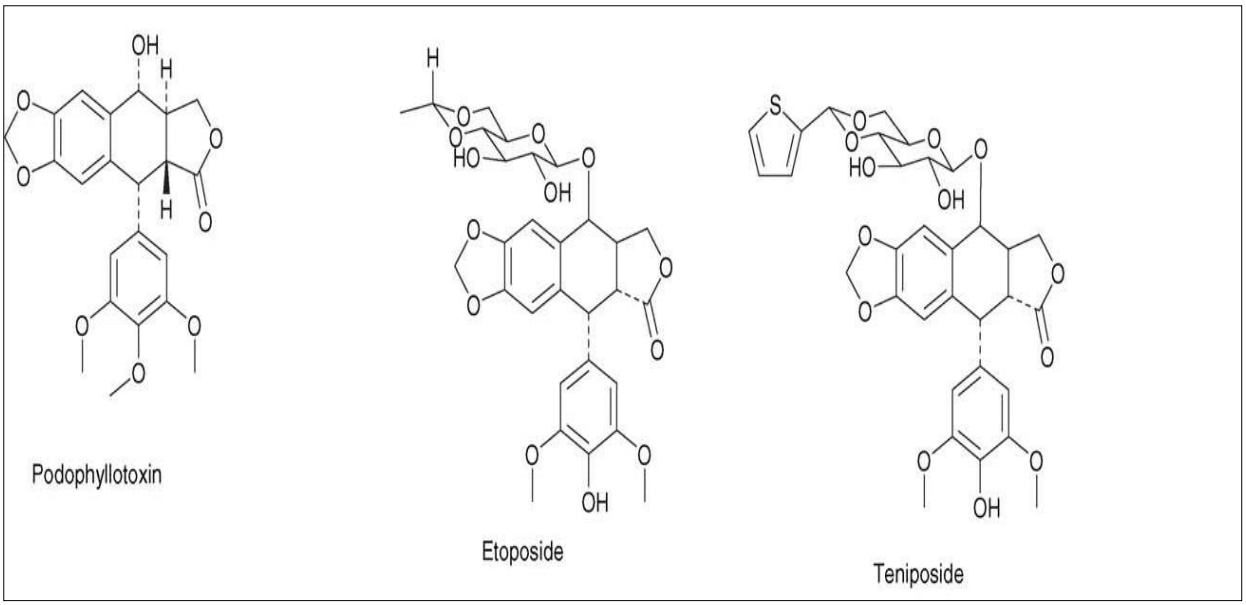


**Figure 2: chemical structure of podophyllotoxin and derivatives**

Etoposide (VM 26) and teniposide (VP 16-213), which are semi-synthetic derivatives of the natural product, epipodophyllotoxin (an isomer of podophyllotoxin) are used clinically as anticancer agents. The *Podophyllum* species, *Podophyllum peltatum* Linnaeus (commonly known as the American mandrake or Mayapple), and *Podophyllum emodii* Wallich from the Indian subcontinent, have a long history of medicinal use, including the treatment of skin cancers and warts. Etoposide and teniposide are used in the treatment of lymphomas and bronchial and testicular cancers.

**Taxanes**

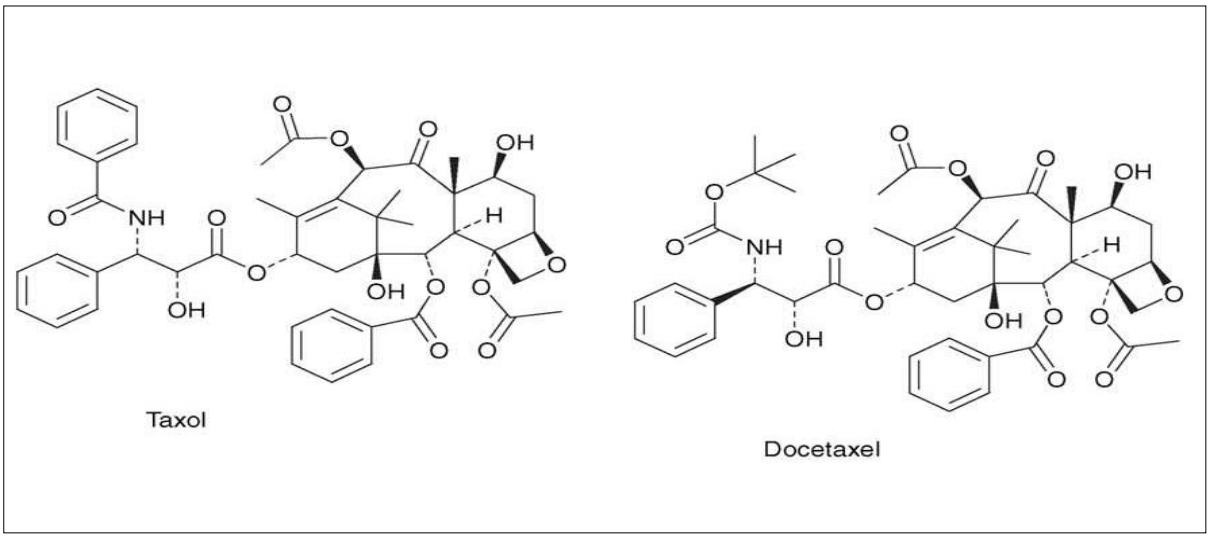

**Figure 3: chemical structure of taxanes; taxol and Docetaxel**

Taxanes form another plant derived chemotherapeutic agents. Paclitaxel (taxol) initially was isolated from the bark of the Pacific Yew plant, *Taxus brevifolia* Nutt. Various parts of *Taxus brevifolia* and other *Taxus* species (e.g., *Taxus Canadensis* Marshall, *Taxus baccata* L.) were being used by several Native American tribes for the treatment of some non-cancerous conditions, while the leaves of *Taxus baccata* are used in the traditional Indian (Ayurvedic) medicine system in the treatment of cancer. Baccatins an abundant precursor of paclitaxel, as well as active paclitaxel analogs, such as docetaxel (Taxotere), are major, renewable natural source of this important class of drugs. Paclitaxel is used in the treatment of breast, ovarian, and non-small cell lung cancer (NSCLC), and also Kaposi sarcoma, while docetaxel is primarily used in the treatment of breast cancer and NSCLC.

**Camptothecin**

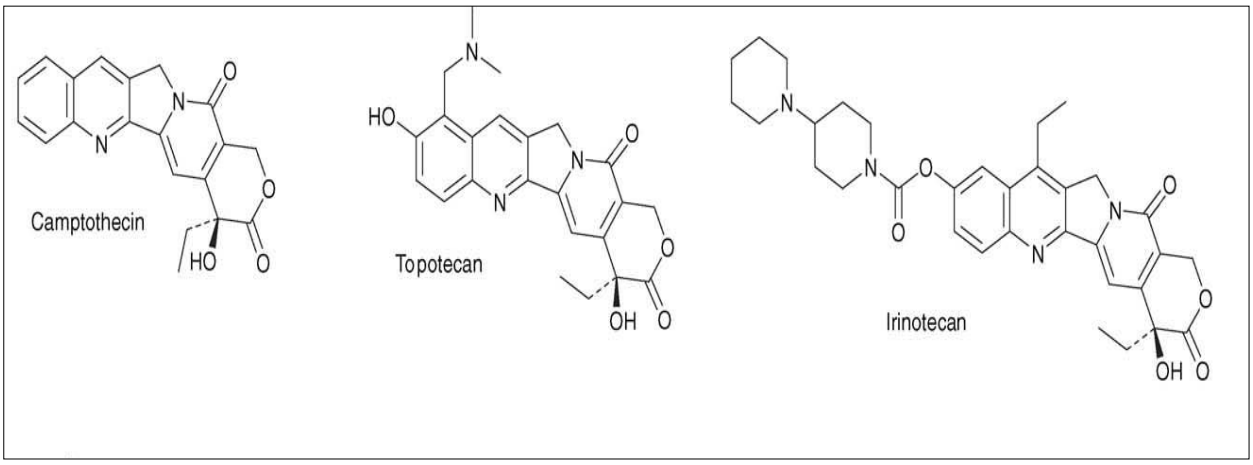


**Figure 4: chemical structure of Camptothecin and derivatives**

Camptothecin, was isolated from the Chinese ornamental tree, *Camptotheca acuminata* Decne (Nyssaceae). [15] Camptothecin (as its sodium salt) was introduced to clinical trials by the NCI in the 1970s, but later it was withdrawn because of its marked urinary bladder toxicity, but extensive research led to the development of more effective derivatives, Topotecan and irinotecan (CPT-11; Camptosar). Topotecan is used for the treatment of ovarian and small cell lung cancers, while irinotecan is used for the treatment of colorectal cancers.

**Common Herbs With Anticancer Activity**

**Allium sativum (Garlic)**

In traditional medicine garlic is a well known remedy to treat various ailments and Hippocrates is the one who recommended garlic usage for cancer therapy. The Garlic extract is found to inhibit growth of cancers of the breast, bladder, skin, colon, oesophagus, stomach and the lung. *Allium sativum* contains more than 100 biologically useful secondary metabolites, like alliin, alliinase, allicin, Sallyl-cysteine (SAC), diallyldisulphide (DADS), diallyltrisulphide (DATS) and methylallyltrisuphide. Recent studies have shown that bioflavonoids quercetin and cyanidin present in garlic are responsible for its antioxidant properties. Ajoene, a sulphur containing compound, found in garlic oil, has the potential to inhibit mutagenesis. Garlic inhibits genesis as well as growth of cancer by enhancing activity of the natural killer cells and the macrophages. Studies have revealed that garlic increases count of the suppressor T cells and makes the lymphocytes more cytotoxic to cancerous cells. Garlic also inhibits metastasis by preventing adhesion of the circulating cancerous cells to the blood vessels. The Garlic extract protects DNA from the damaging effect of carcinogens, enhances activity of detoxifying enzymes, speeds up excretion of chemical carcinogens and activates immunity of the body. [16]

**Curcuma Longa (Turmeric)**

Turmeric has been shown to suppress the development of stomach, breast, lung, and skin tumors. [17] Its activity is largely due to the antioxidant curcumin (a diferuloylmethane), which has been shown to be an effective anti-inflammatory agent in humans. [18] The anticancer effect of curcumin has been demonstrated in all the steps of cancer development, i.e. initiation, promotion and progression of cancer. Curcumin suppresses mutagenic effect of various mutagens including cigarette smoke condensates, 7, 12-dimethylbenz (a)anthracene (DMBA) and benzopyrene. Curcumin is found to decrease levels of urinary mutagens. Studies are suggestive that turmeric inhibits production of nitrosamine thereby enhances natural antioxidant functions of the body. It also increases levels of glutathione and other non-protein sulphhydryls.

**Withania somnifera (Ashwagandha)**

*Withania somnifera* roots have been used as a valuable drug for many ailments in Indian traditional system of medicine. It contains withanolides, which possess immuno-modulatory activity. Withaferin Aand withanolide D found in *Withania somnifera* are known to inhibit growth of cancer. An *in vitro* study showed withanolides from *Withania somnifera* inhibited growth in human breast, central nervous system, lung, and colon cancer cell lines comparable

to doxorubicin. *Withania somnifera* is known to enhance the therapeutic effect of radiotherapy. [7]

**Glycyrrhiza glabra (Liquorice)**

The liquorice plant contains about 8% of glycoside called glycyrrhizin, which is a sweet substance. Dried root and underground stem is being used for medicinal purposes. Glycyrrhizin specifically reduces the activity of enzymes that break down prostaglandin E and has anti-ulcer effects. Liquorice shows anti-infective and anticancer properties. Chemicals derived from liquorice have shown anticancer activity in animal studies and in laboratory cultures of human cancer cells. Additionally, liquorice has some ability to improve functioning of the immune system. [19]

**Plumbago zeylanica (Chitrak or leadwort)**

Plumbago zeylanica is a popular medicinal herb throughout Africa and Asia. The roots of *P. zeylanic* have been used in Indian medicine for more than 2,500 years for treatments of various ailments. Plumbagin, a naphthoquinone present in its roots has been shown to exert anticancer and antiproliferative activities in animal models and in cell culture. Plumbagin is reported to induce cancer cell specific apoptosis in breast cancer cells. [10]

**Targets Of Action Of Herbal Drugs**

Natural compounds fight cancer by various mechanisms which are significantly different from that of conventional chemical drugs. Herbal drugs strengthen the immune system, prevent the spread of cancer cells through inhibition of angiogenesis or growth of new blood vessels to the cancer cells, detoxify the body and prevent further toxic build-up in the body, quench free radicals that cause mutational changes that lead to cancer formation and support all targeted organs. They create an unfavorable environment for cancer growth where a high level of oxygen and temperature, increased metabolic rate, low sugar level and a high alkalinity space in the body exist. [20] Many herbal medicines are widely used as immunomodulators and also as chemopreventive (adaptogenic) compounds. [21] A variety of herbal medicines and plant compounds directly stimulate the innate (Th1) immune response and activates the Natural Killer (NK) cells which directly kill the tumour. [22, 23] These agents can be used to protect bone marrow against the myelosuppressive effect of conventional chemotherapy. Plant-derived compounds fighting cancer by inhibition of protein synthesis, and cell cycle progression blocking are currently under investigation. In recent years, an active ingredient responsible for the immunomodulation of some herbs has been found to be a

form of complex polysaccharides. [24] Direct cytotoxic action of herbal compounds is also proposed as an important mode for its anticancer effect. Many kinds of tumor suppressor genes had been shown to be involved with cell proliferation and apoptotic regulation of cancer cells. Mutations in the p53 gene are frequently found in many human cancers, and the mutation sites are localized in the conserved region of the gene. [25] Other examples of tumor suppressors include retinoblastoma protein (Rb), PTEN (Phosphatase and Tensin homolog deleted on chromosome 10), p21WAF1, p27KIP1 and APC (adenomatous polyposis coli). [26] There might be a substantial relationship between medicinal herbs and tumour suppressors. [27] For *Scutellaria baicalensis* a herb used as an adjuvant to cancer chemotherapy, cell growth arrest and apoptosis are proved as potential mechanisms of cytotoxicity. Increased expression of p53 in the cancer cells lead to enhanced apoptosis. [28] Similarly, *Gleditsia sinensis* thorns are used as a medicinal herb, which shows a decrease in cell growth and an increase in cell cycle arrest during the G2/M-phase. The arrest is correlated with increased p53 levels and down regulation of cyclinB1. [29] Ginsenoside, one of the components in American ginseng herb, increases levels of Bax protein, activating the p53 tumor suppressor and induces cell death. [30] Knockout of p53 dramatically decreases the cell death, suggesting that p53 contributes to apoptosis induced by Ginsenoside in the cancer cells. The honokiol, a component of oriental herb *Magnolia officinalis*, treatment decreases the viability of PC-3and LNCaP human prostate cancer cells in a concentration and time-dependent manner with G0 G1 phase cell cycle arrest. The honokiol-treated PC-3 and LNCaP cells exhibited a marked decrease in the levels of total retinoblastoma protein (Rb), which correlated with the suppression of transcriptional factor E2F1. [31] Licochalcone a novel estrogenic flavonoid isolated from the herb licorice, shows antitumor activity in various human cell lines. Licochalcone also inhibits phosphorylation of pRb, specifically phosphorylation of S780, and reduces expression of transcription factor E2F; cyclins D1, Cdk4, and Cdk6. [32, 33] *In vitro* studies have revealed that the plant compounds, curcumin and resveratrol synergistically inhibit cell growth and induce apoptosis. [34] Molecular targets including phosphorylated Akt, cyclinD1, mTOR, and androgen receptor are down-regulated by the combination of curcumin and resveratrol due to the activation of PTEN, suggesting that some herbs may reduce cancer incidence via the intervention of tumor suppressor gene PTEN. [35] In another study treatment with ethanol extract of *Gleditsia sinensis* thorns on vascular smooth muscle cells leads to a decrease in cell growth by arresting cells in the G2/Mphase of the cell cycle, which is associated with upregulated p21WAF1 protein levels. [36] Since several plants have potential

medical and biological efficacy in patients with neoplasms of various origins, further studies are necessary to evaluate their effects based on the molecular mechanisms.

**Drug Discovery From Herbs**

There are about 119 drugs of known structure that are extracted from plants and used globally in allopathic medicine. Various approaches for the drug discovery from herbs constitute: (a) random selection high chemical screening, (b) random selection followed by biological assays, (c) follow-up of biological activity reports, (d) follow-up traditional or ethnomedicinal use of plants etc. The folk medicines or ethnomedicines are mostly pioneer attempts or phases in the development of modern classic medicines and hence they should be considered cautiously. Drug development process from ethnomedicine begins with a plant taxonomist, ethnobotanist and ethnopharmacologist who gain data and decipher the plants species desired. Drug discovery from herbs has to face many challenges. Phytochemists and pharmaceutical industries should improve both quality and quantity of compounds which enter the drug development process in view of other efforts of drug discovery. The entire process is time-consuming and costlier affair. Lead compound identification is the first step. Lead optimization, inclusive of medicinal and combinational chemistry and clinical trials take a lot of time. The ethnopharmacology knowledge and experiential base thus allows drug research from 'Clinics to Laboratories'- a true 'Reverse Pharmacology' approach. There is another trend that the pharmaceutical research is moving away from single molecule or single target approach to combinations and multiple target approaches. [37] The various aspects coming into account while developing drugs from traditional preparations made from herbs include;

**Quality Control**

Quality control of traditional medicines is a critical and essential issue to be considered in assuring their safety and therapeutic efficacy, and to rationalize their use in healthcare. To meet these, techniques like finger printing and marker compound analysis are nowadays being used to standardize traditional formulations of medicine. [38] Here, concentrations of secondary metabolites, the major constituents of herbal drugs, are studied, providing valued scientific standardization procedures. This technique not only helps in establishing the correct botanical identity, but also in regulating the chemical purity of the herbs. Of these marker compounds, some are therapeutically active, while others though not active, are present in abundance helping in their standardization, for example, withanolides from *Withania*

*somnifera* are therapeutically active marker compounds; on the other hand aegelin from *Aegle marmelos* is not therapeutically active, but its presence is already well established, so it can be used as a marker compound. It is now accepted that qualitative and quantitative analysis of major bioactive chemical components (marker components) of a crude drug constitute an important and reliable part of quality control protocol, since any change in quality of the drug directly affects the constituents. Such analyses need to be developed for every aspect of single herbs and polyherbal extracts. [39, 40]

**Quality Assurance**

Quality assurance is an integral part of traditional medicine, ensuring that it delivers the required quantity of quality medicament. For this good manufacturing practices (GMP) particularly for herbal drug are to be carefully attended right from field cultivation, preparation of formulations such as powder, extract, pure components, etc. In this era of worldwide herbal drug revolution, there is a demand to implement GMP in the production of medicinal products from natural resources. According to these norms, natural drugs must contain one or more herbal ingredients and it should not be harmful under specified conditions of application. Currently, there are about 900 licensed manufacturing units for different Indian systems of medicine producing different natural product formulations. [40]

**Safety Studies**

Many in the general public believe that modern drugs are dangerous chemicals with side effects, while herbals are natural and safe. In fact, some herbs can also be dangerous and even cause serious diseases leading to death, if used inappropriately. People may tend to consume herbal products along with prescription medicine without their therapist's knowledge, which may lead to herb-drug interaction, via cytochrome enzymes. Manufacturer's evaluation of these products for toxicology, preclinical and clinical data is not compulsory, and hence is not yet subject to standard pharmaceutical criteria for safety many a times. Various countries have produced regulatory requirements concerning safety and assessment of potential interactions between phytoconstituents and conventional medicines. Herbal practitioners, researchers and manufacturers should also take the initiative to make pharmacovigilance function properly in the same way as doctors reporting reactions to synthetic pharmaceuticals. By providing evidence that certain herbal health risks are absent or negligibly small, pharmacovigilance can also be reassuring. [41]

**Future Prospects**

With the identification of an increasing number of molecular targets associated with particular cancers, high throughput screening of compounds against a range of such targets now forms the basis of anti-cancer drug discovery. A promising approach to utilise plant derived molecules is to investigate their potential as "warheads" attached to monoclonal antibodies specifically targeted to epitopes on tumors of interest. [42] Experiments on cell lines and in animals demonstrated that herbal drugs anticancer role is by inducing apoptosis and differentiation, enhancing the immune system, inhibiting angiogenesis and reversing multidrug resistance. However, the mechanism of the anticancer role has not yet been fully elucidated. Further research is needed to explore the molecular mechanism of herbal drugs. Though it has been demonstrated that herbs are helpful against cancer, especially useful in improving survival and quality of life in patients suffering from advanced cancer, the lack of controls and reporting bias have been severe flaws. Potential herb-drug interactions should be taken into consideration if multiple drugs are prescribed simultaneously. Researchers must pay attention to the scientific rigor of studies of herbal drugs in the future to improve the status. [43]

## CONCLUSION

Natural products have inspired many developments in drug discovery. There are many historical examples in which the natural product has not just been the medicinal product but has also helped to reveal a novel aspect of drug isolation. Plants have been a prime source of highly effective conventional drugs for the treatment of many forms of cancer, and while the actual compounds isolated from the plant frequently may not serve as the drugs, they provide leads for the development of potential novel agents. As new technologies are developed, some of the agents which failed earlier clinical studies are now stimulating renewed interest. [10] With the rapidity of modernization and industrialization, a lot of ethnic information used in healthcare is in danger of being lost. Hence, the time is right to develop and document traditional knowledge and medicine, and so further assist in developing suitable drugs for various ailments in the future.

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