ETHNOPHARMACOLOGICAL REVIEW OF TRADITIONAL HERBAL PLANTS FOR ANTICANCER ACTIVITY

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ABSTRACT

Medicinal herbs have been on the forefront whenever we talk about anticancer remedies. Herbal medicines have a vital role in the prevention and treatment of cancer. With advanced knowledge of molecular science and refinement in isolation and structure elucidation techniques, various anticancer herbs has been identified, which execute their therapeutic effect by inhibiting cancer-activating enzymes and hormones, stimulating DNA repair mechanism, promoting production of protective enzymes, inducing antioxidant action and enhancing immunity of the body. Here we covered the plants used previously and recently identified for treatment of cancer and to reduce the pains during the treatment of cancer. Cancer is a disease that begins in the cells of the body. Side effects of allopathic drugs and development of resistance to currently used drugs for infectious diseases have led to increased emphasis on the use of plant materials as a source of medicines for a wide variety of human ailments. In the cancer drug discovery program, a paradigm based on ethnobotanical and ethnopharmacological data would be more economic and beneficial for identifying potential anti-cancer molecules than mass screening of plants species. With the advent of combinatorial chemistry and high throughput screening, however, even greater progress may be expected with natural product leads. A number of promising new agents are in clinical development based on selective activity against career related molecular targets. This paper deals with some important medicinal plants used as an anti-cancer activity.

KEYWORDS: Cancer, Cancer types, Causes, anticancer agents, Medicinal herbs, Herbal medicines, Cancer treatment.
1. INTRODUCTION

Cancer
Cancer refers to a group of disease that result from the abnormal growth in the cells. These cells divide and produce new cells in an uncontrolled way that can spread throughout the body and cause damage to essential organs. When cancer spreads to other parts of the body, this is called metastasis. Metastases can occur when cancer cells enter the bloodstream or lymph system. These systems circulate all over the body and allow the cells to travel.[1]

Cancer Statistics worldwide
An estimated 12.7 million new cancer cases were diagnosed worldwide in 2008. Lung, female breast, colorectal and stomach cancers were the most commonly diagnosed cancers, accounting for more than 40% of all cases. Worldwide, an estimated 7.6 million deaths from cancer occurred in 2008.

Cancer Scenario in India
In India, the International Agency for Research on Cancer has estimated that about 635,000 people died from cancer in 2008, representing about 8% of all estimated global cancer deaths and about 6% of all deaths in India. These compiled data show that the number of male, female and the total cancer patients in 2004 were 390809, 428545 and 819354 respectively. The number of male and female cancer patients increased continuously up to 2009, with 454842, 507990 and 962832 cases for male, female and total cancer patients, respectively. Similarly, 462408 male cancer patients and 517378 female cancer patients were recorded, with a total number of 979786 patients in 2010. Thus, it is clear from this data that the number of cancer cases has increased gradually with time. (Figure 1) In India, there is an increment of 10,000 new cancer patients every year and the number of total victims stands at about 25 lakh all over according to “Indian Council of Medical Research” (ICMR).

![Figure-1: Year wise total cancer prevalence in India.](image_url)
United States

International Agency for Research on Cancer (IARC) estimated 12.4 million cancer patients in USA by the end of the year 2012, with that number expected to double by 2020 and almost triple by 2030. From 1970 to 2000, the global cancer rate has been doubled. Estimated new cases and deaths from cancer in the United States in 2012: New cases: 1,638,910 (does not include non-melanoma skin cancers) .Deaths: 577,190 nearly half of all men and one-third of all women in the United States suffer from cancer during their lifetimes. Today, millions of people are living with cancer.\(^1\) The number of new cancer cases and deaths in the United States in 2013(Figure-2).\(^2\)

![Graph showing estimated new cases and deaths by sex, United States, 2013](image)

**Figure-2: Ten Leading Cancer Types for the Estimated New Cancer Cases and Deaths by Sex, United States, 2013**

There are four main types of cancer: (Figure-3)

1. **Carcinomas**, the most common types of cancer, arise from the cells that cover external and internal body surfaces. Lung, breast, and colon are the most frequent cancers.
(2) **Sarcomas** are cancers arising from cells found in the supporting tissues of the body such as bone, cartilage, fat, connective tissue, and muscle.

(3) **Lymphomas** are cancers that arise in the lymph nodes and tissues of the body's immune system.

(4) **Leukemias** are cancers of the immature blood cells that grow in the bone marrow and tend to accumulate in large numbers in the bloodstream.\(^3\)

![Different Kinds of Cancer](image)

**Figure-3: Common types of cancer**

**Development of Cancer**

Cancer can develop in people of all ages, but it is more common in people over 60 years old. One of every three people will develop cancer at some point in their lives. With long age, the risk of developing cancer is increasing. The development of cancer is a long process that usually starts with genetic changes in the cells, and continues in the growth of these cells over time. Differentiation -characteristic feature distinguishing one cell from another; 2) Proliferation -the rapid and repeated production of new cells; 3) Mitotic -cell division resulting in the formation of two new nuclei each having the same number of chromosomes as the parent nucleus. (Figure 4)
Tumors (Neoplasms)

The gradual increase in the number of dividing cells creates a growing mass of tissue called a "tumor" or "neoplasm." Tumors ultimately increase in size because new cells are being produced in greater numbers than needed. As more and more of these dividing cells accumulate, the normal organization of the tissue gradually becomes disrupted. Tumors are classified as being either benign or malignant. Benign tumors are tumors that cannot spread by invasion or metastasis; hence, they only grow locally. Malignant tumors are tumors that are capable of spreading by invasion and metastasis. By definition, the term "cancer" applies only to malignant tumors. (Figure-5)
Difference between cancer cell and normal proliferating cell

Cancer cells multiply without differentiate. Normal functional cells do not divide. Normal proliferating cell divides to produce missing normal functional cells, and stop to divide after producing enough normal functional cells to replace the missed. Normal proliferating cell differentiate after divide, or switch to dormant. Cancer cell does not. Cancer cell continues to divide to produce more and more without doing any repairing. (Figure-6)

![Figure-6: Difference between normal cell and cancer cell](image)

Those useless cells compete nutritional resource, produce large quantity of lactate acid, and damage surrounding normal cells. Besides the outrage division, the difference also includes:

**Morphology (pathological difference in cancer cells and normal cells)**

In general, there is less than 0.1% difference in genome between cancer cell and normal functional cell. Cell is structured with DNA, RNA, protein, lipid, carbohydrate, water, etc. Protein is one of the most important molecules in the cell to participate very complex biochemistry reactions. Gene can influence cell biology only when the gene is active, RNA and protein are synthesized, and changing biochemistry occurs. In general, besides the differences above, all cancer cells of all cancer types are very similar to their normal proliferating cells in genome, morphology, and biochemistry pathways. Also cancer cell can be dormant in the body for years. To survive, cell needs fuel to produce energy. Energy generation pathway is fundamental biochemistry pathway for all living cells.
In 1920’s, Dr. Otto Warburg and his research group first observed cancer cells use fermentation for energy efficiency, other than respiration, which produces CO$_2$ and water.$^{[4-6]}$ Cancer cells get their energy through fermentation (Glycolysis), other than respiration (Oxidative Phosphorylation). This is the fundamental difference of cancer cells from other cells. Lactate fermentation is the hallmarks of cancer cell.$^{[7-10]}$ Normal functional cells get their energy mainly through respiration. Normal proliferating cells depend on fermentation to divide, but switch to respiration after division during differentiation. Cancer cells stick to fermentation. Normal cell can live with lactate fermentation or oxidative respiration according to its living environment, and switch to one or the other, as it needs. Both cancer cell and proliferating cells mainly depend on lactate fermentation to divide, i.e. the high ratio of fermentation to respiration is essential for cell division. When the respiration goes up, normal proliferating cells stop divide and begin to differentiate to normal function cell or stay dormant. Cancer cells stick with fermentation without increasing the respiration pathway. (Figure-7)

![Figure-7: Pathological difference in cancer cells and normal cells.](image)

**Causes of cancer**
Different types of cancer have different causes and are likely to depend on many factors. Some cancers are more common than others, and chances for survival vary among different types. Most cancers have known causes from chemical, environmental, genetic,
immunologic, or viral origin. The causes of cancer are very complex, involving both the cell and factors in the environment. Much progress has been made in identifying possible causes of cancer which includes:

1. **Viral and Chemical Carcinogen.** Being exposed to certain chemicals, metals, or pesticides can increase the risk of cancer. Any chemical that is known to cause cancer is called a carcinogen. Asbestos, nickel, cadmium, uranium, radon, vinyl chloride, benzidine, and benzene are examples of well-known carcinogens. These may act alone or along with another carcinogen, such as cigarette smoke, to increase the risk of cancer. For example, inhaling asbestos fibers increases the risk of lung diseases, including cancer, and the cancer risk is especially high for asbestos workers who smoke. Long-standing infection with the hepatitis B or C viruses can lead to cancer of the liver. One of the herpes viruses, the Epstein-Barr virus, causes infectious mononucleosis and has been linked to non-Hodgkin lymphomas and nasopharyngeal cancer. People with human immunodeficiency virus (HIV) have greater increased risk of developing several cancers, especially Kaposi sarcoma and non-Hodgkin lymphoma. Human papilloma viruses (HPVs) have been linked to many cancers, especially those of the cervix, vulva and anus. Some head and neck cancers (mostly the tongue and tonsils) are linked to the high-risk types of HPV, too.

2. **Tobacco.** The most common carcinogens are those present in cigarette smoke. Tobacco smoke is known to contain at least 60 carcinogens and 6 developmental toxicants. In addition to being responsible for 80 to 90% of lung cancers, cigarette smoking is also associated with cancers of the mouth, pharynx, larynx, esophagus, pancreas, kidney, and bladder.

3. **Ionizing radiation.** Certain types of radiation, such as X-rays, rays from radioactive substances, and ultraviolet rays from exposure to the sun, can produce damage to the DNA of cells, which might lead to cancer.

4. **Heredity.** Certain types of cancer occur more frequently in some families than in others, indicating some inherited predisposition to the development of cancer. Even in these cases, however, environment plays a part in the development of cancer.

5. **Oncogenes and tumor suppressor genes** During the 1970s, two particularly important families of genes related to cancer were discovered: oncogenes and tumor suppressor genes.

a. **Oncogenes:** These genes cause cells to grow out of control and become cancer cells. They are formed by changes or mutations of certain normal genes of the cell called proto-
oncogenes. Proto-oncogenes are the genes that normally control how often a cell divides and the degree to which it differentiates (or specializes in a specific function in the body). (BRCl, BRCll)

b. Tumor suppressor genes: These are normal genes that slow down cell division, repair DNA errors, and tell cells when to die (a process known as apoptosis or programmed cell death). When tumor suppressor genes don’t work properly, cells can grow out of control, which can lead to cancer.

6. Diet
High-fat, high cholesterol diets are proven risk factors for several types of cancer such as those of the colon, uterus and prostate. Obesity may be linked to breast cancer among older women as well as to cancers of the prostate, pancreas, uterus, colon and ovary.

7. Immune system
Problems of immune systems are more likely to cause some types of cancer. This group includes individuals with
1. Organ transplantation and use of drugs that suppress the immune system
2. HIV infection
3. in born rare medical syndromes which affect immunity.

8. Hormonal imbalance
Some hormones are responsible for the development of cancer by promoting cell proliferation. Such cancer includes cancer of the breast, endometrium, prostate, ovary, and testis, thyroid and bone cancer.

9. Occupational exposure
It includes high-risk occupations such as uranium miners, asbestos factory workers, certain chemical plant workers, and workers in nuclear power plants etc.

10. Reproductive Factors
The reproductive factors category refers mostly to women’s risk factors. For example, the risk of breast cancer goes up if a woman does not have children before the age of 30. Sexually transmitted diseases also increase the risk of cervical cancer.
11. Sedentary Lifestyle
Not moving around much during the day may increase the risk of cancer. The body’s own defenses work better when you exercise and maintain an ideal weight. Moderate exercise such as walking or climbing a flight of stairs can help.

12. Alcohol/Drugs
Alcohol contributes to the risk of developing cancer. People who drink or use of abuse drugs may increase the overall risk for cancer.

13. Pollution
Although, environmental pollution is a major cause of cancer, in fact few cancers have been found to be caused by pollution, but research is still ongoing. The cause of many cancers is not known. Other factors that interact to increase the risk of cancer are age, hormonal balance, response to stress, and status of the immune system.

Cancer symptoms: Depending upon the specific type of tumour symptoms may vary however there are some the common symptoms that are observed in the cancer such as:
1. Thickening or lump in the body
2. Cough or hoarseness that does not go away
3. Obvious change in a wart or mole
   4. Changes in bowel or bladder habits
5. Unexplained bleeding or discharge
6. Any sore that does not heal
7. Unusual upset stomach or difficulty swallowing

Treatment of Cancer
Even with cancers that cannot be cured, symptoms are often greatly diminished by treatment. Treatment options, which depend on the stage and type of cancer, include:
a) Surgery
Surgery is the oldest form of cancer treatment. Advances in surgical techniques have allowed surgeons to operate on a growing number of patients and with good outcomes. Surgery offers the greatest chance for cure for many types of cancer, especially those that have not spread to other parts of the body. The side effects of surgery depend mainly on the size and location of the tumor, and the type of operation.
The more common types of cancer surgeries are prophylactic surgery, diagnostic surgery, staging surgery, curative surgery, and palliative surgery.\(^\text{[11]}\)

**b) Radiation therapy**
Radiation therapy uses high-energy rays to kill cancer cells. Several types of radiations are used in the therapy. Some patients receive a combination of treatments.

**External radiation:** The radiations are given from the outside of the patient’s body.

**Internal radiation** (implant radiation): The radiation comes from radioactive material placed in seeds, needles, or thin plastic tubes that are put in or near the cancer tissue.

c) **Chemotherapy**
Chemotherapy includes the use of drugs that kill cancer cells. Most patients receive chemotherapy by oral route or through intravenously. Either way, the drugs enter the bloodstream and can affect cancer cells all over the body. Chemotherapy is usually given in cycles. People receive treatment for one or more days. Then they have a recovery period of several days or weeks before the next treatment session.\(^\text{[12]}\)

d) **Biological therapy**
Immunotherapy is the treatment that uses immune system to fight cancer. Biological therapy is known as “Immunotherapy”, and “biotherapy”.\(^\text{[13]}\)

Types of biological therapy include the use of some tools such as interferon, interleukin, cytokines, and vaccines.\(^\text{[14]}\) There are many kinds of biological therapy. Some common ones that are used in cancer management the following:-

**BCG** treats bladder tumors or bladder cancer.
**IL-2** treats certain types of cancer.
**Interferon alpha** treats certain types of cancer.
**Rituxan** or **Rituximab** treats non-Hodgkin's lymphoma.
**Herceptin** or **Trastuzumab** treats breast cancer.

e) **Hormone therapy**
Several types of cancers are derived from hormonal responsive tissues, including the cancer of breast, prostate, endometrium, and adrenal cortex.\(^\text{28}\) Hormonal therapy prevents the
cancer cells to use the hormones which are essential for various types of cancers to grow. There are mainly two types of drugs used in Hormonal therapy:

1. Aromatase inhibitors
2. Hormone receptor antagonists
3. Antiandrogens

Side effects of allopathic drugs and development of resistance to currently used drugs for infectious diseases have led to increased emphasis on the use of plant materials as a source of medicines for a wide variety of human ailments. The compounds derived from plants and their semi-synthetic as well as synthetic analogs have been important source of several clinically useful anti-cancer agents. A number of promising new agents are in clinical development based on selective activity against cancer related molecular targets.

**TABLE 1: Some Medicinal Plants used as Anti-cancer agents**

<table>
<thead>
<tr>
<th>S.No</th>
<th>Botanical Name</th>
<th>Family</th>
<th>Main active components</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acororus calamus</td>
<td><em>Araceae</em></td>
<td>Asarone, eugenol, methyl eugenol, Palmitic acid</td>
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<td>2</td>
<td>Agrimonia pilosa</td>
<td><em>Rosaceae</em></td>
<td>Agrimonolide, flavnoid, tannin, triterpene and coumarin</td>
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<td>3</td>
<td>Alstonia scholaris</td>
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<td>Linalool, cis and trans linalool oxides, α-terpineol</td>
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<td>4</td>
<td>Andrographis paniculata</td>
<td><em>Acanthaceae</em></td>
<td>Flavonoid, andrographin &amp; andrographolid</td>
<td>[24-28]</td>
</tr>
<tr>
<td>5</td>
<td>Annona glabra</td>
<td><em>Annonaceae</em></td>
<td>annonacin, annonacione, corossolone, annomontacin, squamosine</td>
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<tr>
<td>6</td>
<td>Apium graveolens</td>
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<td>phthalide constituents, luteolin, linolenic acid, psoralen and oleic acid</td>
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<td>Asparagus racemous</td>
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<td>Shatavarns, essential oils, asparagin, arginine, tyrosine, resin, kaempferol, queretin and rutin</td>
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<td>8</td>
<td>Azadirachta indica</td>
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<td>Tetranortriterpenoids, azadirone, epoxyazadiradione, nimbin gedunin, azadiradione and deacetylnimbin</td>
<td>[53-62]</td>
</tr>
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<td>9</td>
<td>Allium sativum</td>
<td><em>Liliaceae</em></td>
<td>Alliiin, allicin alliiin, allinase, S-allylcysteine, (SAC), diallyl disulphide, (DADS), diallyltrisulphide (DATS) and methylallyltriisuphide.</td>
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<td>10</td>
<td>Actinidia chinensis</td>
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<td>Aloe ferox, Aloe barbadenis</td>
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<td>Aloe-emodin, emodin, aloin, acemannan</td>
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<td>Betulin</td>
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<td>Catharanthus roseus</td>
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<td>Vinblastine, Vincristine, Ajmalicine Reserpine and Alstonine</td>
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<td>Lysine</td>
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<td>Colchicum luteum</td>
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<td>Colchicines demecolcine</td>
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<td>Combretastatin</td>
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<td>Euphorbia neriifolia</td>
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<td>Leguminosae</td>
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<td>35</td>
<td>Mentha arvensis</td>
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<td>36</td>
<td>Ochrosia elliptica</td>
<td>Apocynaceae</td>
<td>Ellipticine and 9-methoxy ellipticine are pyridocarbazole alkaloids</td>
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<td>Ginsenosides, Panaxosides</td>
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<td>Picrosides I, II, III and kuttoside</td>
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<td>Podophyllum hexandrum</td>
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<td>Withania somnifera</td>
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<td>42</td>
<td>Zingiber officinale</td>
<td>Zingiberaceae</td>
<td>Ginger Curcumin, gingerenoneA, Gingeols</td>
<td>[128-129]</td>
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**DISCUSSION AND CONCLUSION**

Science has long acknowledged the value of healing substances found in nature, such as digitalis, aspirin, penicillin, insulin, steroids, etc. There has been a resurgence of interest, both scientifically and popularly, in the utilization of natural approaches. Experiments on cell lines and in animals demonstrated that herbal drugs anticancer role 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. Although the clinical trials showed that herbs were helpful against cancer, these outcomes require further confirmation with rigorously controlled trials, many clinical trials focusing on the anticancer effects of herbal formulas have been conducted. Though many of them 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. Plants have been a prime source of highly effective conventional drugs for the treatment of many forms of cancer. Plants provide active constituents which acts directly against various ailments or indirectly by providing leads for the development of potential novel agents. Large number of herbal species has been used traditionally or as folk medicines against cancer. Many of them have been studied scientifically and proved to be beneficial anti-cancer agents. In medicine, particularly in the field of cancer, the use of herbs is increasingly enhanced especially with the excessive use of synthetic drugs and awareness of their toxicity, which contributed in oncology, leading to a
favorable reconsideration of the medicinal practices made from natural herbal. Despite the divergent bioactivities of the plant medicines against various diseases, active components of most plant extracts have not been elucidated thoroughly, due their complex mixtures. The ability of agents to attach to carrier molecules directed to specific tumors, shows highly cytotoxic natural products to the tumors. A better understanding of the characteristics of tumor cells has recently led to the development of more targeted treatments, and therefore generally less toxic. In conclusion, the use of naturally occurring molecules in the treatment of cancer has greatly contributed to the improvement of the therapeutic efficacy of drugs used today in cancer chemotherapy. This article provides the knowledge of anti-cancer medicinal plants.

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