Review Article

Comparative Anticancer Activity of Selected Medicinal Plants Highlighting Their Molecular Mechanisms

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ABSTRACT

Cancer is a complex disease having high mortality rates and limited effectiveness of conventional treatments like radiation therapy and chemotherapy, which have severe side effects and resistance. In search of safe and effective alternatives, interest in medicinal plants increases. Anti-cancer activities highlighting the molecular mechanisms exhibited by the medicinal plants such as *Curcuma longa, Phyllanthus emblica, Moringa oleifera, Zingiber officinale, Catharanthus roseus, Artemisia annua, Nigella sativa,* and *Annona muricata* are compared here. These medicinal plants contain many bioactive compounds (such as curcuminoids, flavonoids, alkaloids, terpenoids, and polyphenols, etc.) and show anticancer activity through various mechanisms and pathways, such as Curcuma longa, which contains a high amount of curcumin, modulating multiple signalling pathways such as NF-κB, PI3K/Akt, and MAPK, which help to manage tumour progression. *Phyllanthus emblica* induces apoptosis, while Moringa oleifera modulates oxidative stress and inflammatory responses, Zingiber officinale suppresses cancer cell proliferation and induces apoptosis, Catharanthus roseus has chemotherapeutic properties, Artemisia annua helps in cancer cell apoptosis, Nigella sativa has anti-inflammatory and antioxidant mechanisms, and Annona muricata has cytotoxic effects on cancer cells. Comparison between these medicinal plants helps us to find potential applications in cancer prevention and treatments.

Keywords: Cancer, Anticancer activity, Medicinal plants, Phytochemicals.

INTRODUCTION

Cancer, which is a very serious medical emergency and a health crisis, causing millions of deaths every year. It is a type of complex group of diseases characterised by uncontrolled cell growth, invasion of surrounding tissues, or metastasis to distant organs.[1] Genetic mutations, lifestyle choices, environmental factors, etc., can be cause for development of cancer.[2] Lung cancer, breast cancer, colorectal cancer, prostate cancer, liver cancer, etc., are a few common types of cancer that have different characteristics and biological mechanisms.[3]

As the modern healthcare system and technology evolve day by day, they help with early detection, diagnosis, and treatment, but still worldwide cancer is a leading cause of death. Nowadays, different treatments like surgery, chemotherapy, radiation therapy, immunotherapy, and targeted drug therapies help to deal with cancer with improved survival rates, but they also have limitations. Likewise, chemotherapy and radiation therapy can cause severe side effects, such as nausea, fatigue, immunosuppression, organ toxicity, etc., and in the long term, many types of cancers develop resistance to these treatments.[4] For these reasons, exploring alternative treatments became crucial, especially from natural sources.

Medicinal plants are a valuable gift from our mother nature, which has given us many valuable phytochemical compounds having high pharmacological validity throughout ages. Many modern drugs obtained from medicinal plants have immense medicinal potential. The success of plant-derived anticancer agents, like paclitaxel obtained from Taxus brevifolia and vinblastine obtained from Catharanthus roseus, has encouraged further research to find out medicinal plants with potential anticancer properties.[5] Natural compounds have diverse mechanisms of action, such as apoptosis induction, inhibition of tumour cell proliferation, suppression of angiogenesis, or modulation of key signalling pathways, which can help to prevent the progress of cancer.[6]

Among various medicinal plants known for their anticancer activity, *Curcuma longa, Phyllanthus emblica, Moringa oleifera, Zingiber officinale, Catharanthus roseus, Artemisia annua, Nigella sativa,* and *Annona muricata* are known for their promising anticancer effects.[7] They have a wide range of bioactive compounds such as curcuminoids, flavonoids, alkaloids, terpenoids, and polyphenols, which show anticancer potential in many preclinical and clinical studies.[8] Different studies show that these compounds can target multiple cancer-related pathways and help to treat cancer. Comparative studies of these medicinal plants are essential to compare their effectiveness, mechanisms of action, etc., to find out potential therapeutic applications. Comparison is essential to identify the most reliable plant-derived compounds, which can be useful for further development, which is clinically useful for treatments. The aim of this review is to assess and compare the anticancer activities of these selected medicinal plants based on existing scientific evidence. Understanding their

therapeutic potential can contribute to the ongoing search to analyse naturally effective anticancer agents having fewer side effects and more medicinal potential.

Risk factors

It is usually unknown why one person develops cancer while another does not. However, research has shown that some risk factors may increase a person's chance of developing cancer.

The following is a list of the most studied known or suspected cancer risk factors-

1. Age- Growing older is the biggest risk factor for cancer.[9] According to the national institute of cancer the rate of formation of all different types of cancer in India by 2022, from fewer cases less than 200 cases per 25,000 population in age categories under 30, to over 700 cases per 110,000 population in age groups of 60-64, overall cancer prevalence rates increase steadily with age but decreases minutely from ages 70-74.[9,10]

2. Alcohol- Chance of developing cancers of the oesophagus, mouth, liver, throat, breast and larynx (voice box) can all rise by drink alcohol. the risk of getting cancer is directly proportional to the amount of alcohol consumed.[11] Those who use alcohol and tobacco have a significantly increased risk of developing cancer.[11]

3. Diet- Unhealthy diet leads to increase the risk of cancer and other chronic disease and also obesity. It is possible that certain nutrients or dietary components are linked to higher or lower cancer risk has already been the subject of numerous studies. Research on animal models and laboratory-grown cancer cells has occasionally shown that certain substances (such as fluoride, alcohol, and acrylamide) may be carcinogenic.[11,12,13]

4. Hormones- A class of female sex hormones known as oestrogens is known to cause cancer in people. These hormones have been linked to an increased risk of some types of cancer, despite the fact that they have vital physiological roles in both males and females.[9,10] For example, a woman's risk of breast cancer may be increased by taking combined menopausal hormone therapy, which consists of oestrogen and progestin, a synthetic form of the female hormone progesterone. Only women who have had a hysterectomy are treated with menopausal hormone therapy, which uses oestrogen alone and raises the risk of endometrial cancer.[10]

5. Immunosuppression- For the purpose of to safeguard the organ from being rejected by the body, many recipients of organ transplants take drugs that suppress the immune system. These immunosuppressive medications weakens the immune system's power to identify and eliminate cancerous cells or combat infections that lead to cancer. HIV infection also impairs immunity and raises the risk of some types of cancer. Transplant recipients are more likely to develop a wide range of malignancies. The four most prevalent cancers among transplant patients are lung, kidney, and liver cancers, as well as non-Hodgkin lymphoma (NHL), which is more common in transplant recipients than in the overall population. Epstein-Barr virus (EBV) infection can induce NHL, while chronic hepatitis B (HBV) and hepatitis C (HCV) virus infection can cause liver cancer.[13,14]

6. Infectious agents- Some infectious agents, such as bacteria, viruses, and parasites, can either cause cancer or raise the risk of developing it. Certain viruses have the ability to interfere with signalling, which typically controls cell division and growth. Additionally, some diseases impair immunity, which reduces the body's capacity to fight off infections that cause cancer. Additionally, a number of bacteria, viruses, and parasites can cause chronic inflammation, which can eventually result in cancer.[14]

7. Sunlight- Both of them the sun and tanning salons emit ultraviolet (uv) light. Early skin ageing and skin damage that can result in skin cancer are caused by exposure to UV radiation. Limiting sun exposure, particularly between mid-morning and late-afternoon, and avoiding tanning beds and other UV radiation sources are important for people of all ages and skin tones.[13]

8. Tobacco- One of the main causes of cancer and cancer-related deaths is tobacco usage. Because tobacco products and secondhand smoke include numerous chemicals that damage DNA, people who use tobacco products or are frequently around environmental tobacco smoke, also known as secondhand smoke, are more likely to develop cancer.[10] Numerous cancers are brought on by tobacco use, including acute myeloid leukaemia and cancers of the lung, larynx (voice box), mouth, oesophagus, throat, bladder, kidney, liver, stomach, pancreas, colon, and rectum, as well as the cervix.[11] Users of smokeless tobacco, such as snuff or chewing tobacco, are more likely to develop pancreatic, esophageal, and oral malignancies.Tobacco use has no safe threshold.[11,13]

9. Cancer causing substances- Changes to specific genes that affect how our cells work and thus creating cancer. When DNA replicates during cell division, some of these genetic alterations naturally take place. Others, however, are caused by exposures to the environment that harm DNA.[13] Substances like the compounds in tobacco smoke or radiation like the sun's UV rays can be included in these exposures.[11]

   Some cancer-causing exposures, like tobacco smoke and sunlight, can be avoided by people. Some, however, are more difficult to avoid, particularly if they are present in the food we eat, the water we

drink, the air we breathe, or the supplies we use for our occupations.[11] Researchers are looking at the exposures that can lead to or cause cancer. People may be able to avoid dangerous exposures if they are aware of which ones exist and where they can be discovered.[13]

The following chemicals have been identified as known human carcinogens by the National Toxicology Program (NTP) in its 15th Report on Carcinogens.

Nickel, Radon, Silica, Crystalline, Solar Radiation, Soots, Aflatoxins, Alcoholic Beverage Consumption, 4-Aminobiphenyl Analgesic Mixtures Containing Phenacetin, Aristolochic Acids, Arsenic and Inorganic Arsenic Compounds, Asbestos, Azathioprine, Benzene, Benzidine, Beryllium and Beryllium Compounds, Bis(chloromethyl) Ether and TechnicalGrade Chloromethyl Methyl Ether, 1,3Butadiene, 1,4Butanediol Dimethanesulfonate, Cadmium and Cadmium Compounds Chlorambucil 1(2Chloroethyl)3(4methylcyclohexyl)1nitrosourea, Chromium Hexavalent Compounds, Coal Tars and CoalTar Pitches, Coke, Oven Emissions, Cyclophosphamide, Cyclosporin A, Diethylstilbestrol Dyes Metabolized to Benzidine (Benzidine Dye Class), EpsteinBarr Virus, Erionite Estrogens, Steroidal Ethylene Oxide, Formaldehyde.[13]

10. Obesity- People who are obese may be more likely to develop cancers of the breast (in women who have gone through menopause), colon, rectum, endometrial (uterine lining), oesophagus, kidney, pancreas, and gallbladder, among other cancers. On the other hand, maintaining a healthy weight, exercising, and eating a balanced diet may help lower the chance of developing various types of cancer.[11,12]

11. Radiation- Ionising radiation, a type of radiation with specific wavelengths, has sufficient energy to harm DNA and cause cancer. Radon, x-rays, gamma rays, alpha, beta, and neutron particles are examples of ionising radiation. It has not been discovered that lower-energy, non-ionizing radiation, such visible light and cell phone energy, can cause cancer in humans.[13]

12. Chronic inflammation- Chronic inflammation occurs when the inflammatory process does not stop when it should and can start even in the absence of injury. The cause of the ongoing inflammation is not always understood. Chronic inflammation can be brought on by persistent infections, aberrant immune responses to healthy tissues, or diseases like obesity. Chronic inflammation has the potential to damage DNA over time and result in cancer.[14]

Types of cancer

Cancers are categorised based on the type of cell they originate in. There are five major groups. They are-

1. Carcinoma- carcinoma cancers are the type of cancers that are originated from the epithelial tissues. Epithelial tissues are located on the lining of internal organs, skins and glands. Adenocarcinoma (like breast, lungs, colon), basal cell carcinoma (like skin) and squamous cell (lungs, cervix, oesophagus) carcinoma are among the several subtypes.[15]

2. Sarcoma- Sarcomas are also known as connective tissues cancer as it starts in the connective tissues. The connective or supporting tissues, such as bone, cartilage, fat, muscle, or blood vessels, are the origin site of sarcoma cancers. Connective tissues also include things like tendons, cartilage, bones, and fibrous tissue that supports organs. There are two main types- the bones' sarcomas & Delicate tissue sarcomas.[16]

3. Leukaemia- Leukaemia occurs in blood-producing organs. It begins in the bone marrow and Leukaemia is a type of white blood cell malignancy. The bone marrow produces too many white blood cells which have not fully grown, they do not function as intended. Leukaemias are the most prevalent form of cancer in children. Acute Lymphoblastic Leukemia, Chronic Lymphocytic Leukemia are examples of leukaemias.[17]

4. Myeloma and lymphoma- Malignancies are also termed as myeloma and lymphoma cancers, it begins in cells of the immune system. Lymphoma is a type of cancer that starts in the cells or lymph glands of the lymphatic system. Because of the body's widespread lymphatic system, lymphoma can start practically anywhere. Hodgkin's, Non-Hodgkin's are examples of this types of malignancies.[17]

5. Brain and spinal cord cancers- Malignancies of the central nervous system, including brain and spinal cord tumours and Cancer. It start in the cells of the brain and spinal cord. The brain is composed of billions of nerve cells called neurones. Glial cells are the source of the most common type of brain cancer (glioma). **Glioblastoma multiforme, Astrocytoma, Meningioma** are few examples of brain and spinal cord cancers.[18]

6. Germ cell cancer- Germ cells malignancies are the cancers of reproductive cells. It can occurs in both male and female in the cells responsible for formation of sperm or ovum respectively. malignancies can also form in gonads that is testes in male and ovaries in female. Testicular Germ Cell tumours(**Seminoma** and **Non-seminomatous germ cell tumours,** Ovarian Germ Cell Tumours (**Dysgerminoma**, **Immature Teratoma**, **Endodermal Sinus Tumour) are among the several subtypes of germ cells tumours.**[19]

Mechanism of cancer

A number of steps are involved in the development of cancer, including:

1. Cellular Mutation- Genetic mutations result from heavy metal compounds replacing vital organic components in cells. These mutations alter the structure of DNA and RNA, impairing regular cellular

processes and ultimately resulting in the development of cancerous cells. Over time, cancer cells have mutations that increase their aggression. They make ineffective utilisation of DNA repair processes, which raises the rate of mutations.[20]

2. Cell Proliferation- When essential organic components in cells are replaced by heavy metal compounds, genetic changes occur. These mutations change the way DNA and RNA are structured, which disrupts normal cellular functions and eventually leads to the growth of malignant cells. Mutations in cancer cells throughout time make them more aggressive. They use DNA repair mechanisms inefficiently, which increases the frequency of mutations.[20]
3. Altered Cell Signaling- In order to improve nutrient absorption, cancerous tissues alter their surroundings to get oxygen and vital nutrients, they make wide channels, which speeds up their growth.[20]
4. Avoidance of Apoptosis- When normal cells are harmed or no longer required, they undergo apoptosis by inhibiting pro-apoptotic proteins (Bax, Bak) and upregulating anti-apoptotic proteins (Bcl-2, Bcl-xL), cancer cells become resistant to programmed cell death and are able to outlive healthy cells. They can proliferate and develop into cancerous tumours because of this resistance.[21,22]
5. Metastasis and Spread- Cancer cells separate from the main tumour and move via the lymphatic or circulatory systems. They cause secondary tumour growth by invading distant organs.[22]

Table 1: List of selected medicinal plants having anti-cancer activity

Scientific Name	Common Name	Family	Part Used	Phytochemical Constitute	Mechanism of Action	Type of Cancer Treated	Ref.
Curcuma longa	Turmeric, Halud, Haldi, Haridra	Zingiberaceae	Rhizome	Curcuminoids (curcumin, demethoxycurcumin, bisdemethoxycurcumin), Volatile oils (turmerone, atlantone, zingiberence), Flavonoids, Tannins, Saponins, Alkaloids.	Induces apoptosis by Inhibiting NF-kB signalling. Supress angiogenesis by downregulating VEGF. Modulates p53 and Bcl-2 proteins to induce cell cycle arrest.	Breast cancer, Colorectal cancer, Prostate cancer, Lung cancer.	23 - 26
Phyllanthus emblica	Amla, Amloki, Awla, Amalaki	Phyllanthaceae	Fruit	Polyphenols (gallic acid, ellagic acid), Tannins (emblicanin A, emblicanin B), Flavonoids (quercetin, kaempferol), Vitamin C, Alkaloids.	Induces apoptosis using mitochondrial pathway. Reduces oxidative stress and inflammation by scavenging free radicals. Inhibit proliferation through downregulation of Pl3K/Akt/mTOR pathway.	Liver cancer, Lung cancer, Brest cancer, Colon cancer.	27 - 29
Moringa oleifera	Drumstick Tree, Sahjan, Sojne data, Shevga	Moringaceae	Leaves, seeds, bark	Isothiocyanates (moringin, benzyl isothiocyanate), Flavonoids (kaempferol, quercetin), Glucosinolates, Alkaloids, Saponins.	Induces apoptosis using caspase activation. Supress tumour growth by inhibiting STAT3 and NF-kB pathways. Inhibits angiogenesis and metastasis through downregulation of MM-9.	Breast cancer, Pancreatic cancer, Colon cancer, Liver cancer.	30 - 32
Zingiber officinale	Ginger, Adrak, Allam, Ale, Ada, Inji	Zingiberaceae	Rhizome	Phenolic Compounds (gingerol, shogaol, paradol, zingerone), Flavonoids, Terpenoids, Alkaloids.	Induces apoptosis via mitochondrial and death receptor pathways. Inhibit cancer cell proliferation through suppression of NF-kB and MAPK pathways. Suppresses metastasis and invasion by downregulating MMPs.	Colon cancer, Ovarian cancer, Breast cancer, Prostate cancer.	33 - 35
Nigella sativa	Black seed, black cumin, fennel flower, kalonji, nigella, roman coriander	Ranunculaceae	Seed	Thymoquinone (TQ), thymol (THY), thymohydroquinone (THQ), dithymoquinone (DTQ), essential oils, Fixed oils, proteins, saponin, alkaloids, Alpha (α)-hederin.	Induces apoptosis by upregulating the pro-apoptotic genes caspases and Bax and downregulating the anti-apoptotic gene Bcl-2. Disrupt mitochondrial membrane, causing cytochrome release and activation of caspases 8, 9, and 3. Apoptosis via the c-Jun NH2-terminal kinase and p38 mitogen-activated protein kinase	Cervical cancer, Renal cancer, Prostate cancer, Lung cancer, Skin cancer, Breast cancer,	36 - 41

					pathways. Inhibits the Akt pathway, block Akt phosphorylation. Deactivate NF-kappa B by preventing its nuclear translocation. Oncogenic and anti-apoptotic proteins such IAP1, IAP2, XIAP, Bcl-2, Bcl-xL, and survivin will be produced. It enhances antioxidant enzyme activity (SOD, CAT, GPx).	Blood cancer, Pancreatic cancer, Colon cancer, Hepatic cancer.	
Catharanthus roseus	Madagascar periwinkle, old maid, rose periwinkle, sadabhar, vinca	Apocynaceae	Leaves, roots	Catharanthin, Catharoseumine, Vinleurosin, vindesine, vinflunine, Vinposidin, vinorelbine, vinblastine and vincristine and Rosindin.	Bind between two tubulin heterodimers, leading to mitotic arrest. Disruption of microtubules halts cell division in the metaphase stage. Block the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway. Triggers the c-Jun N-terminal kinase (JNK) pathway. Alkaloids immediately kill cancer cells by forming paracrystals, It interacts with calmodulin to stop the proliferation of cancer cells, Disrupt metabolism of amino acids.	Breast cancer, Lung cancer, Leukaemia.	42 - 46
Annona muricata	soursop, graviola, guanabana, pawpaw, sirsak	Annonaceae	leaves, seeds, Root, stem, branch, fruit's pulp	Alkaloid are atherosperminine, argentinine, coclaurine, isocoreximine, reticuline, and xylopine. annonaceous acetogenins (AGEs) Isolated polyphenols are catechin, kaempferol, and procyanidins, and quercetin.	Blocks mitochondrial Complex I. Trigger activation of caspase-3, caspase-7, and caspase-9 and upregulating pro-apoptotic proteins (Bax and Bad) and downregulating anti-apoptotic proteins (Bcl-2 and Bcl-xL). Cell cycle arrest in G0/G1 and G2/M phases. Akt/mTOR signalling, Wnt signalling and β-catenin is inhibited. Metastasis inhibition by reducing epithelial-mesenchymal transition (EMT).	Breast cancer, Colon carcinoma, Head and Neck cancer, Liver cancer, Lung carcinoma, Prostate carcinoma, Pancreatic cancer.	47 - 51
Artemisia annua	Annual wormwood, sweet annie, Sweet wormwood, Qinghao	Asteraceae	Stems, leaves	Artemisinin, arteannuin B, chrysosplenol D, and casticin. Flavonoids and polyphenols.	Stop growth of cancer cells in G1 or G2/M phase of cell cycle. Apoptotic hypodiploid cell formation, loss of mitochondrial membrane potential, and caspase 3 activation.	Breast cancer, Colon cancer, pancreatic cancer, Prostate cancer, Lung cancer.	52 - 55

CONCLUSION

Most of the population believe in natural remedies for therapeutic purpose worldwide. From the very beginning Indians relays on mother nature for treatment and cure. Among them, *Curcuma longa, Phyllanthus emblica, Moringa oleifera, Zingiber officinale, Catharanthus roseus, Artemisia annua, Nigella sativa, and Annona muricata* were most commonly use in different parts of the world for the treatment and prevention of cancer, which have also been through many trials and proved to have anti cancer property in them. Comparing according to their effectiveness as anti cancer agent from higher to lower these eight plants namely *Curcuma longa, Phyllanthus emblica, Moringa oleifera, Zingiber officinale, Catharanthus roseus, Artemisia annua, Nigella sativa, and Annona muricata* gone through preclinical and some clinical studies it is seen that *Catharanthus roseus* is most potent then *Nigella sativa, and Annona muricata also shows high* anti cancer property but lower than *Catharanthus roseus, Curcuma longa* shows moderate to high anti cancer activity whereas *Annona muricata, Zingiber officinale* and *Phyllanthus emblica* shows moderate anti cancer property and lastly *Moringa oleifera* shows low to moderate anti cancer property. Mostly they work by apoptosis of cancer cells and by changing the structure of mitochondria. These plants are high in antioxidant, alkaloids and flavonoids which mainly responsible for their anti cancer effect. Vinca alkaloids like vincristine and vinblastine of *Catharanthus roseus* were mainly responsible for their anti cancer effect and *Curcuma longa's* chemical constituent curcuminoid is responsible for apoptosis of cancer cells by Inhibiting NF-kB signaling

pathway. All these plants shows no such side effect during clinical trial results.

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