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Review Article

An overview of medicinal plants as anticancer agents

Sofia Khanam[1,*], **Aman Prakash**[2]

[1]*Dept. of Pharmacology, Calcutta Institute of Pharmaceutical Technology & AHS, Uluberia, Howrah, West Bengal, India*
[2]*Dept. of Molecular and Cellular Engineering, Sam Higginbottom University of Agriculture, Technology and Sciences Naini, Prayagraj, Uttar Pradesh, India*

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ABSTRACT

Due to the lack of conventional therapies and the severe side effects of chemotherapy, cancer is a major public health concern across the world. After cardiac disorder, it is the second leading cause of death globally. Since ancient times, medicinal plants have been utilized to cure a variety of diseases. Natural products play an essential role in the battle against cancer and serve as a useful access source for the development and testing of novel therapeutic agents. The discovery and development of anticancer drugs can be aided by medicinal plants which contain various bioactive secondary phytochemicals viz. Alkaloids, phenolics, flavonoids, carotenoids, and other secondary metabolites. The therapeutic plants and their bioactive constituents exerted anticancer effects by induction of apoptosis, removing free radicals and antioxidant effects, inhibition of angiogenesis, and cell cycle arrest. This review explains an overview of potential therapeutic plants, including a brief description of their pharmacological effect and mechanism of action.

1. Introduction

Cancer is a leading cause of death, affecting more than one-third of the world's population. It is the leading cause of death in the world, accounting for more than 20% of all deaths.[1] In both developed and developing countries, cancer is a serious public health concern. It is a type of cancer in which the body's cells develop abnormally and cause death. Normal cells are generally invaded and destroyed by cancer cells.[2] Every year, more than 10 million new cases of cancer are scrutinized, according to the World Health Organization (WHO), and statistical trends predict that this number will double in the decades.[3] Cancer is the second prevalent cause of mortality worldwide, consumed the lives of 10 million people in 2020. Cancer diagnoses are expected to rise by 50% from 14 million to 21 million, while cancer deaths are expected to rise by 60% from 8 million to 13 million. Lung cancer (1.69 million deaths), stomach cancer (754000 deaths), colorectal cancer (774000 deaths), liver cancer (788000 deaths), and breast cancer (571000 deaths) are the most prevalent kinds of cancer death. The number of cancer cases is predicted to climb by around 70% in the future decades, with the majority of deaths occurring in low and middle-income nations.[4] It is extremely difficult to pinpoint the exact aetiology of cancer. Tobacco use, environmental pollutants, alcohol intake, infectious agents, customary practices, and lifestyles are some of the most well-known causes of this disease.[5]

Medicinal plants continue to be an important therapeutic aid in the treatment of human diseases since prehistoric times.[6] It is estimated that roughly 80-85 percent of the worldwide population relies on traditional medicines for their primary health care requirements, and it is expected that plant extracts or bioactive principles are used

* *Corresponding author*.
E-mail address: sofiakhanam786@gmail.com (S. Khanam).

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extensively in traditional therapy.[7] Medicinal plants are known to contain a wide range of immunomodulatory and antioxidant activities, as well as anticancer characteristics. Both non-specific and specific immunity is stimulated by these substances. They may improve the host's resistance to infection by re-establishing physiological balance and conditioning the body tissues.[8] The anticancer properties of numerous medicinal plants are being used to discover lead constituents that can stop cancer from spreading. Secondary metabolites in medicinal plants include flavonoids, alkaloids, terpenoids, and steroids, all of which have diverse pharmacological characteristics. Various therapeutic plants show a prospective role in the inhibition of cancer cell proliferation.[9,10] Therefore this review provides an overview of various medicinal plants and their major bioactive constituents used for the treatment of cancer.

2. Cancer

Cancer is a type of disease categorized by the uncontrolled development and spread of aberrant cells. It can result in death, if the spread of cancer cells known as metastasis, is not controlled. Many external (tobacco, radiation, chemicals, and infectious organisms), as well as certain internal factors (hormones, inherited mutations, immune conditions and random mutations), causes cancer.[11] Cancer has a wide range of causes that are complicated and only partly understood. Certain illnesses, dietary variables, obesity, a lack of physical exercise, and exposure to environmental contaminants are all known to raise the risk of cancer.[12] These factors may interact to begin or enhance carcinogenesis in the human body, leading to cancer the main cause of mortality.[13] Due to cancer, 10 million people died in 2020, and more than 19 million individuals are affected.[14] For the appropriate functioning of the bodily system, normal cells proliferate in a regulated manner. Cancer arises when cells grow uncontrollably or abnormally, and it is not limited to a particular organ, but may also spread to other tissues. Mostly, cells can detect and repair any damage to the DNA molecule.[15] When normal cells are injured, they tend to self-destruct. When a cell can no longer heal itself, it enters apoptosis. A tumor is a term used to describe an abnormal cell mass. A benign tumor develops locally and does not spread, but a malignant tumor spreads quickly and invades adjacent tissues, a process known as metastasis.[16] Malignant tumors can spread through the bloodstream or lymphatic system to other tissues such as the lungs, liver, brain, bones, and other organs. Only some metastatic cancers can be cured, while others are incurable.[17] More than 100 types of cancers are there, but mainly most common types of cancers are skin cancer, breast cancer, lung cancer, liver cancer, colon cancer, lymphoma, stomach cancer, prostate cancer, cervical cancer (Figure 1). The most common types of cancer in males are prostate cancer, colorectal cancer, lung cancer, and stomach cancer. The most common types in females are breast cancer, cervical cancer, colorectal cancer, and lung cancer.[18]

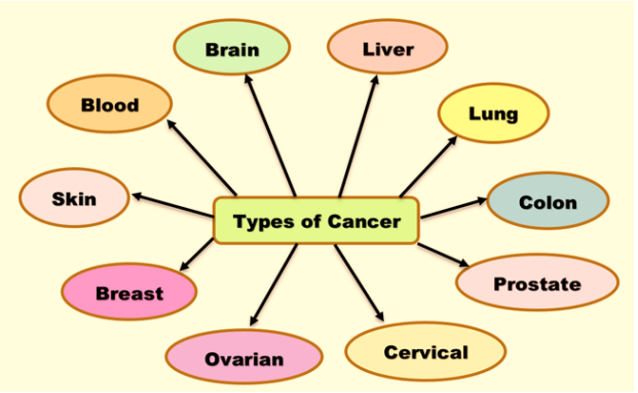


Fig. 1: Types of cancer

2.1. *Causes of cancer*

In the late 1800s, several ideas were proposed by various scientists to establish the origins of cancer.[19] Cancer was thought to be caused by displaced embryonal tissue by Lobstein and Recamier, and subsequently Cohnheim, although Virchow argued that persistent irritation was a major cause of cancer.[20] Viruses were later identified as one of the major causes of cancer based on a few experimental pieces of evidence.[21] All of these studies concluded that cancer is a multifaceted sickness, with a complex web of causes and there is no single factor identified for any type of cancer (Figure 2). The following are some of the factors that damage DNA and are known to cause cancer:

1. Gene mutations
2. Poor immune system
3. Exposure to UV rays and air pollution are two major environmental concerns
4. Helicobacter pylori (H. pylori), Hepatitis B virus (HBV), Hepatitis C virus (HCV), Human papillomavirus (HPV), and Epstein-Barr virus are examples of microbiological infections
5. Unhealthy Habits (smoking, high alcohol intake, tobacco use, exposure to chemicals, obesity)
6. Intake of nonsteroidal anti-inflammatory medicines (NSAID) over a prolonged period

2.2. *Cancer pathophysiology*

On a cellular level, cancer development (Figure 3) is thought to be a multi-step process including mutation and selection for cells with increasingly higher proliferation, survival, invasion, and metastasis.

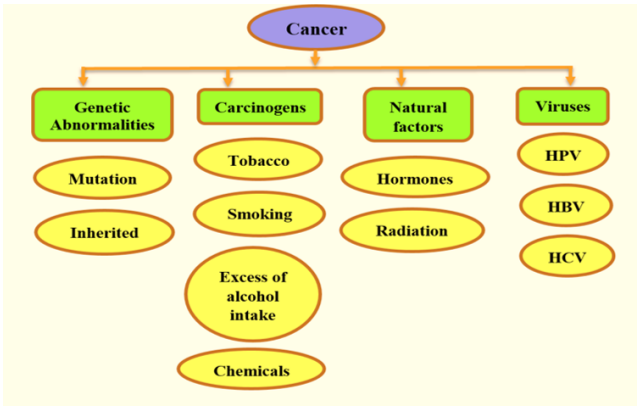
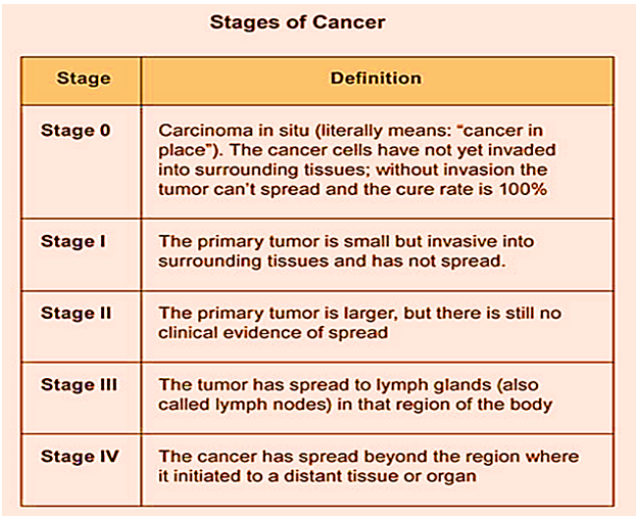


Fig. 2: Cancer-causing agents



Stages of Cancer

Stage	Definition
Stage 0	Carcinoma in situ (literally means: "cancer in place"). The cancer cells have not yet invaded into surrounding tissues; without invasion the tumor can't spread and the cure rate is 100%
Stage I	The primary tumor is small but invasive into surrounding tissues and has not spread.
Stage II	The primary tumor is larger, but there is still no clinical evidence of spread
Stage III	The tumor has spread to lymph glands (also called lymph nodes) in that region of the body
Stage IV	The cancer has spread beyond the region where it initiated to a distant tissue or organ

- **Mutation and tumor initiation:** A genetic change causes a mutation in a single cell, which causes that cell to proliferate abnormally, resulting in a tumor cell.
- **Cell proliferation and Tumor progression :** As more mutations arise among the tumor population, tumor development continues. Mutated cells have a selective advantage over normal cells in that they proliferate and divide quickly. As a result, the progeny of a cell with an extra mutation will become dominant in the tumor population.
- **Clonal selection and malignancy:** Tumor cell proliferation results in a new clone of tumor cells with a faster growth rate or other characteristics (such as survival, invasion, or metastasis) that provide them a selection advantage. The method is known as clonal selection. Clonal selection persists throughout tumor growth, resulting in tumors that grow faster and become more aggressive.
- **Metastasis:** Metastasis is a complicated process in which cancer cells break out from the main tumor and travel to other parts of the body via the bloodstream or lymphatic system. The cells continue to expand in other locations, eventually forming secondary tumors made up of cells that are similar to the original tissue. The capacity of tumors to metastasis, such as pancreatic cancer and uveal (iris, ciliary body, or choroid of eye) malignancies, is a major factor in their lethality. Many fundamental questions about metastatic tumor clonal structures, phylogenetic relationships among metastases, the scale of ongoing parallel evolution in metastatic and primary sites, how the tumor disseminates, and the role of the tumor microenvironment in determining the metastatic site remain unanswered[22].

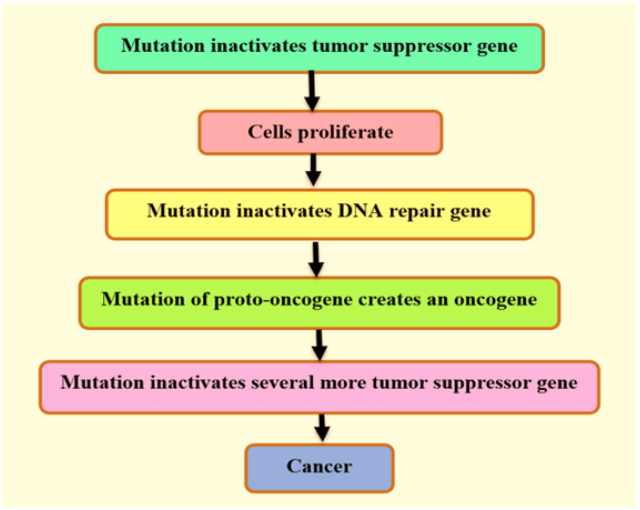


Fig. 3: Development of cancer

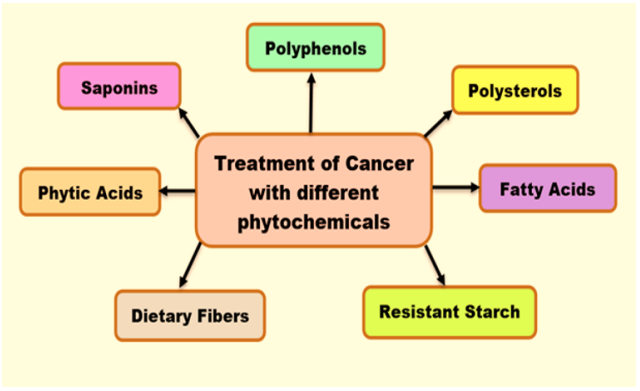


Fig. 4: Different phytochemicals used in the treatment of cancer

2.3. Stages of cancer

"Staging" refers to the process of identifying the severity of cancer. Patients may be prescribed different medications depending on their stage of cancer. Cancer is divided into five phases, each with its own set of characteristics and symptoms.[23] These are tabulated as under:

Table 1: Anticancer activity of various medicinal plants and their derived bioactive constituents with themechanism of action.

S. No.	Medicinal Plants (Common name)	Family	Parts of the plant used	Active Constituents	Mechanism of Action	Ref
1	Curcuma longa (Turmeric)	Zingiberaceae	Rhizomes	Curcumin	Induces apoptosis	24
2	Zingiber officinale (Ginger)	Zingiberaceae	Rhizomes	Curcumin, gingerenone A, gingerols, zingerone	Suppress and arrest the G0/G1-phase, reduces DNA synthesis, and induces apoptosis	25
3	Withania somnifera (Winter cherry, Ashwagandha)	Solanaceae	Roots	Withaferin A, D	Inhibits growth & spread of various cancers	26
4	Allium Sativum (Garlic)	Liliaceae	Bulbs	Allicin, alliin, allixin	Enhances the activity of macrophages and inhibits metastases	27
5	Catharanthus roseus (Madagascar periwinkle)	Apocynaceae	Dried whole plants	Vinblastine, vincristine	Act as an anti-mitotic and anti-microtubule agent	28
6	Glycyrrhiza glabra (Liquorice)	Leguminosae	Extract of plant	Glycyrrhizin	Inhibit abnormal cell proliferation and tumor formation	29
7	Podophyllum hexandrum (Mayapple)	Podophyllaceae	Roots and Rhizomes	Podophyllotoxin, asiragalin, podophyllin.	Arrests multiplication of Cancerous cells by breaking down the microtubule	30
8	Silybum marianum (Milk thistle)	Asteraceae	Leaves	Silymarin, Silybin	Reduces the tumor multiplicity and down-regulates the gene product which is associated with the tumor cells proliferation, angiogenesis, invasion, and metastasis	31
9	Camellia sinensis (Green Tea)	Theaceae	Leaves	Epicatechin, epigallocatechin,epigallocatechin gallate, epigallocatechin-3-gallate	Inhibition of cancer cells proliferation	32
10	Cannabis sativa (Hemp)	Cannabinaceae	Leaves	Cannabinoids, cannabinol,	Induces cancer cell death by apoptosis and inhibits proliferation of cancer cell	33
11	Aloe barbadensis (Aloe vera)	Asphodelaceae	Leaves	Aloe-emodin, Aloin	Inhibit metastasis, enhances the immune system	34
12	Plumbago zeylanica (Ceylon leadwort)	Plumbaginaceae	Leaves	Plumbagin	Induces cell death through apoptosis	35
13	Betula pendula (Silver birch)	Betulaceae	Bark	Betulin, Betulinic acid	Inhibiting cancer cells growth	36
14	Centella asiatica (Asiatic Pennywort)	Apiaceae	Whole plant	Asiaticoside, Asiatic acid	Inhibit cell growth by inducing apoptosis	37

Continued on next page

Table 1 continued

15	Digitalis purpurea (Foxglove)	Plantaginaceae	Leaves	Gitoxigenin, gitoxin	Involved in apoptosis induction	[38]
16	Eugenia aromatic (Clove)	Myrtaceae	Flower buds	Eugenol, carvacrol, thymol, anthocyanins	Inhibit and arrest the growth of cancerous cell	[39]
17	Psidium guajava (Guava)	Myrtaceae	Fruits, Leaves extract	Quercetin 3-glucuronide, d-glucuronic acid, xanthyletin	Inhibits cancer cells through various signaling cascades and induces the growth of tumors	[40]
18	Thuja occidentalis (Arborvitae, white cedar)	Cupressaceae	Leaves extract	Thujone	Decreases the cell viability and showed pro-apoptotic and promotes neoplasia regression	[41]
19	Taraxacum officinale (Dandelion)	Asteraceae	Leaves	Vitamins (A, C, K), calcium, lipotropic choline	Induction of apoptosis in the cancer cells	[42]
20	Olea europae (Olive)	Oleaceae	Leaves and fruits	Oleic acid, oleuropein, pinoresinol, oleanolic acid, maslinic acid	Inhibition of angiogenesis and induction of apoptosis	[43]
21	Ammi visnaga (Toothpick plant)	Apiaceae	Shoot	Visnadine, Quercetin, β-sitosterol, kaempferol, cimifugin, khellol	Cell cycle arrest	[44]
22	Artemisia absinthium (Wormwood)	Asteraceae	Root and shoot	Artemisinin, quercetin, α-pinene, β-pinene, isorhamnetin, myrecene, limonene, linalool, artesunate	Inhibition of angiogenesis and induction of apoptosis	[45]
23	Ferula asafoetida (Asafoetida- Devil's Dung)	Apiaceae	Shoot and resin	Sesquicoumarin, oleic acid, β-sitosterol	Inhibition of mutagenesis and cancer cells proliferation	[46]
24	Tinospora cordifolia (Heart-leaved moonseed)	Menis-permaceae	Whole herbs	Tinosporine, Berberine	Causes activation of macrophages	[47]
25	Azadirachta indica (Neem)	Meliaceae	Leaves	Azadirachtin, nimbolide	Tumor suppressors	[48]
26	Momordica charantia (Bitter Melon)	Cucurbitaceae	Fruits	Momorcharins, momordicine, charantin	Induce autophagy, apoptosis, and cell cycle arrest	[49]
27	Thymus vulgaris (Thyme)	Lamiaceae	Shoot	Thymol, carvacrol	Cell cycle arrest	[50]
28	Garcinia indica (Kokum)	Clusiaceae	Fruits	Garcinol, isogarcinol, Cyanidin-3-glucoside	Induces apoptosis	[51]
29	Lepidium sativum (Cress)	Brassicaceae	Shoot	Vitamins (A, B, C, and E), α-linolenic acid, isothiocyanate, glucosinolates	Cell cycle arrest	[52]
30	Nigella sativa (Black cumin)	Ranunculaceae	Seeds	Thymoquinone, dinitroquinone	Induce apoptosis and cell cycle arrest	[53]

2.4. Herbal Treatment

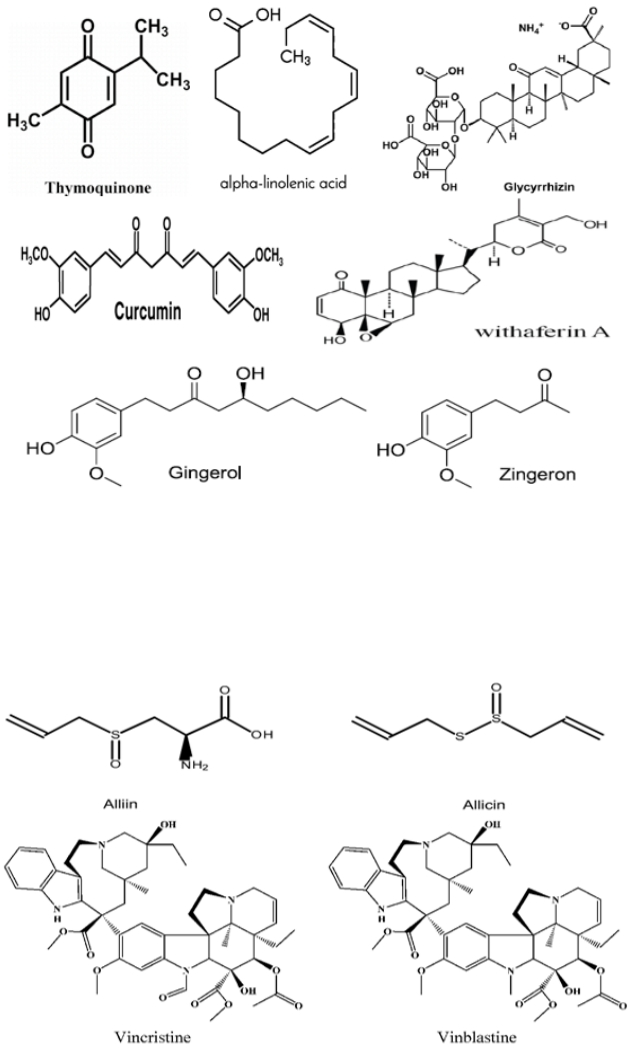
Dietary modifications, cessation of tobacco use, efficient treatment of inflammatory diseases, and the use of nutritional supplements that boost immune functioning are all essential preventative approaches for the majority of malignancies. Chemotherapy, radiotherapy, and chemically generated medications are among the current cancer treatments.[54] Anti-metabolites, platinum analogs, alkylating drugs, and anti-tumor antibiotics are among the most regularly utilized as cancer chemotherapeutic drugs. Chemotherapy and radiation, on the other hand, put patients under a lot of stress and harm their health.

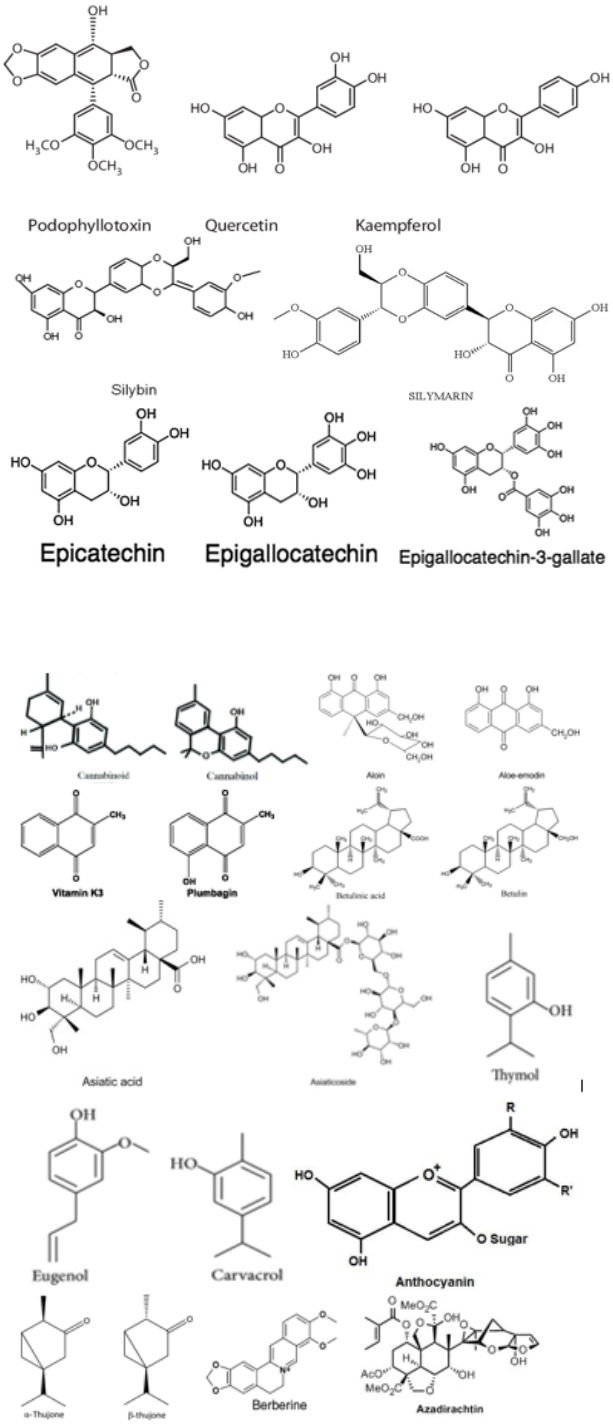
As a result, novel anti-cancer medicines derived from nature, particularly plants, are now being researched. Plants have always been the foundation of traditional medicinal systems, and they have given humans ongoing cures for thousands of years.[55] Plants' therapeutic potential has been discovered over thousands of years of use. The clay tablets include the first written data on hundreds of medicinal herbs, including opium and myrrh. Herbal remedies have been used to treat a variety of ailments for ages. Plant extracts are used in herbal therapy to cure disease and improve the patient's health.[56] The goal of herbal medicine is to restore the body's ability to defend, regulate, and repair itself. Medicinal herbs are used to make a variety of modern medications. Herbal products are available in powdered, pilled, liquid, pasted, or raw form (extract). Certain herbal products tend to cause adverse effects and toxicity. In most situations, the problem emerges as a result of improper usage of herbal goods, mislabeling of plant materials, botanical misidentification, and so on. When taken for incorrect purposes, in high quantities, or improperly prepared, this can be poisonous.[57] Consequently, research into the efficacy of herbal medicines is important to avoid negative consequences. As a result, researchers have developed methods for determining the potential value of plant extracts in the treatment of cancer. Many plants have already been utilized to cure cancer in various forms. Medicinal plants are a storehouse of diverse bioactive chemicals that exhibit a wide spectrum of biological activity, including anti-inflammatory, anti-viral, anti-tumor, and anti-malarial activity.[58] The use of medicinal plants in the manufacture of various medications has been extremely important. Medicinal plants are thought to be a rich source of a wide range of ingredients that can be used in drug development. The anticancer capabilities of numerous medicinal plants are being used to locate a lead ingredient that can stop cancer from spreading. Secondary metabolites in medicinal plants include terpenoids, flavonoids, alkaloids, and steroids, all of which have diverse pharmacological characteristics.[59] (Figure 4).

2.5. Medicinal plants having anticancer activity

Anticancer drugs produced from plants are efficient inhibitors of cancer cell lines. As a result, these plants are in great demand for their ability to produce medically significant compounds. Various more medicinal plants have been utilized for cancer prevention and treatment in traditional cultures all over the world. Curcumin, allicin, vincristine, vinblastine, silymarin, hecogenin glycyrrhizin, berberine, campothecin, gallic acid, and many types of bioactive constituents, which are key active ingredients of plants, have shown promise in the treatment of cancer in the future.[60] Some of the medicinal plants that possess anticancer activity are discussed in Table 1.

2.6. Structures of bioactive constituent that acts as anticancer agents





3. Conclusion and Future Challenges

Cancer consumed the lives of millions of people every year. Various cancer treatments are accessible, but they all have drawbacks such as renal damage, gastrointestinal disorders, and so on, necessitating the development of a new solution to this problem. Given that nowadays more than 50% of medicines are derived from plants so it is crystal clear that natural resources, especially plants could be radically used to find active drugs for cancer treatment. There was been a discrepancy in the past that the use of natural resources, especially plants can be time-consuming. Though nowadays using new techniques has been accelerated active plant compounds extraction and this, in turn, has been used as medicinal plants. The rebirth of medicines created in plants especially ones used for cancer treatment and autoimmunity is remarkable. The number of herbal constituents that have been used to treat cancer is not more than 60 combinations. Since there is little evidence about the helpfulness and safety of plant production compared to products commonly consumed more research can improve the appropriate use of herbal preparations. There are some disadvantages in cancer treatment using chemotherapy, surgery, and radiation therapy that make challenges in treatment for these methods. Chemotherapy repeatedly leaves severe adverse effects and can cause hurt to healthy cells. Radiation therapy will be effective when the tumor location is well known. Surgery will be effective when tumor location and addition are recognized but, when sensitive tissues, such as brain tissue surrounding it, are impossible. Therefore, a new approach in the treatment of cancerous tumors is unavoidable to comment. The use of gold nanoparticles and especially nanoparticles is increased targeting cancer cells. Therefore, investigating the use of these nanoparticles with plant metabolites as a new approach is recommended.

4. Conflict of Interest

The authors declare that there are no conflicts of interest in this paper.

5. Source of Funding

None.

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Author biography

Sofia Khanam, Student https://orcid.org/0000-0002-5201-7387

Aman Prakash, Student

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