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Herbal drugs used in treatment of cancer

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Abstract
Cancer, a leading cause of death worldwide, is a complex and multifaceted disease characterized by uncontrolled cell growth and metastasis. This review explores the potential of herbal medicine in cancer treatment, highlighting the therapeutic benefits and mechanisms of action of various herbal compounds. With cancer being a leading cause of death worldwide, the need for effective and targeted therapies is demanding. Herbal medicine offers a promising option for cancer treatment. Compounds such as *curcumin, Momordica charantia, berberine, resveratrol, garlic, ginger, Catharanthus roseus, and taxols* have demonstrated anti-cancer properties, including anti-proliferative, pro-apoptotic, anti-metastatic, and anti-angiogenic effects. These compounds target multiple signaling pathways, modulating cellular processes and inducing apoptosis in cancer cells. While challenges and limitations exist, herbal compounds hold great promise as adjunctive therapies, enhancing the efficacy of conventional treatments while minimizing side effects.

Keywords: Herbal medicine, cancer treatment, anti-cancer compounds, phytotherapy, curcumin

1. Introduction

Plant-derived materials or products with therapeutic or other human health benefits, which contain either raw or processed ingredients from one or more plants is the definition of herbal medicines as they relate to Complementary and Alternative Medicines (CAM). Raw plant materials, processed plant materials, and herbal medicinal products are all included in this definition of herbal medicines [1]. Many modern medications contain herbal ingredients. In reality, at least one active ingredient in about 25% of US prescription medications comes from plant sources. Some are synthesized to resemble naturally occurring plant compounds, while others are made from plant extracts. Eighty percent of the world's population uses drugs derived from natural sources, according to a World Health Organization (WHO) report [2].

Hippocrates, the father of western medicine, coined the term "cancer" by describing tumors with the Greek word "carcinoma" and "karakinos" [3]. Every country's life expectancy is greatly impacted by cancer, one of the leading causes of death [4]. These cells also invade other tissues. Cancer progress will be slowed down when the amount of DNA damage is limited or perhaps enhanced and repaired by preventing the uncontrolled growth of cancer cells, given the increasing knowledge and developmental motivation of researchers regarding the molecular etiology of cancer. Numerous factors, including genetics, radiation, obesity, sex, race, familial history, low physiological activity, smoking, fiber intake, epigenetics, nutrition, stressful situations, antioxidant consumption, and more, have been known to contribute to cancer [5]. The five main cancer types in men are lung, prostate, colorectal, stomach, and liver cancer; in women, the main cancer types are breast, colorectal, lung, cervix, and stomach cancer. Because it is not detected in its early stages, cervical cancer is a serious form of cancer [6].

There are over 100 known types of cancer. First, each cancer is categorized based on the type of cell that is involved. The National Cancer Institute's (NCI) classification system divides cancer into the following categories:

1. Carcinoma
2. Leukemia
3. Lymphoma
4. Myeloma
5. Central nerve system cancer

Cancer is now regarded as a human tragedy, and the number of deaths from the disease is rising [3]. A number of genetic and epigenetic alterations that interfere with normal cell growth, control, and survival lead to cancer [7]. The type and stage of the disease determine the effectiveness of the many available treatment options. The surgical removal of tumors or malignant tissue, radiotherapy, chemotherapy, and immunotherapy are common forms of treatment [8].

Since ancient times, natural products derived from herbal remedies, medicinal plants, functional foods, and their constituents have been used to treat a variety of illnesses, including cancer. In recent years, research on traditional medicine has become more and more important. In order to deal with inflammation-mediated diseases, new strategies are needed, and natural products may be useful in both preventing and treating these conditions [9]. Numerous technological advancements and studies have been conducted for fighting cancer, including immunotherapy, radiation therapy, chemotherapy, and micro/nanoparticle injections [10]. A significant portion of the use of complementary and alternative medicine (CAM) for cancer treatment comes from Asian nations, particularly China and India. Numerous herbs are used in the majority of Ayurvedic and Siddha herbal preparations that are sold in India to treat a variety of illnesses, including cancer [11].

Table 1: Warning signs of cancer [12]

Symptoms studied		Abbreviations
Focal symptoms: General symptoms:	Non-healing skin lesion	Skin lesion
	Lump/nodule	Lump
	Unusual bleeding	Bleeding
	Pigmented skin lesion	Mole
	Persistent digestive problem	Digestive problem
	Cough/hoarseness of uncertain origin	Cough
	Other symptom suspicious of cancer	Other
	Unintentional weight loss	Weight loss
	Unusual fatigue	Fatigue
	Unusual pain	Pain

2. Causes and Risk Factors of Cancer [13, 14]

1. There are numerous factors that can lead to cancer in various body parts. For example, tobacco use accounts for 22% of deaths, while poor diet, obesity, inactivity, excessive alcohol consumption, and other factors like exposure to ionizing radiation, environmental pollutants, and infections account for 10% of deaths.
2. Hepatitis B, Hepatitis C, Epstein-Barr virus, Helicobacter pylori, human papillomavirus infection, and HIV are among the infections that cause about 15% of cancer worldwide. The genes have changed, at least in part, because of these factors.
3. Between 5 and 10% of cancers are also caused by genetic flaws inherited from the patient's parents.

Medical medications

Food contamination

1. hormones, and reproductive factors
2. Natural, industrial, and medical sources of ionizing radiation; ultraviolet (UV) radiation
3. Immunosuppression
4. Parasites
5. Bacteria
6. Fungi
7. Herbs

3. Complications

The two main causes of death in the US are cancer and heart disease. Many of our patients, particularly the elderly, suffer from both cancer and heart disease because these conditions share a number of risk factors. Additionally, cardiovascular problems may arise from cancer treatments such as chemotherapy or radiation therapy [15].

Chemotherapy-induced heart failure and heart muscle toxicity, especially from anthracyclines and HER-2 receptor antagonists, have gained more recognition and evidence, which has helped guide strategies to reduce the risk of this potentially fatal side effect [16].

Chemotherapy-related vascular complications can arise from "off-target" drug effects or, more crucially, from the substantial overlap between signalling pathways necessary for tumor growth and those necessary for normal vascular function. Chemotherapy-induced vascular toxicity frequently indicates endothelial dysfunction, as evidenced by decreased anti-inflammatory and vascular reparative responses as well as a loss of vasorelaxant effects. These consequences could contribute to the onset and continuation of atherogenesis, thrombosis, and hypertension [16].

By releasing pro-inflammatory mediators, the inflammatory response to a post-operative infection can raise the risk of tumor recurrence in cancer [17].

Oral problems resulting from cancer and cancer therapies are not adequately documented, addressed, or treated. Mucositis, infection, changes in saliva, and neurosensory abnormalities are examples of acute oral complications. Neurosensory abnormalities, changes in saliva, taste, and function, oral and dental infections, and the possibility of dental disease and jaw necrosis are among the complications that survivors face. The quality of life is impacted by these issues [18].

Conditions like stomatitis, infection, bleeding, mucositis, pain, loss of function, and xerostomia are among the oral side effects linked to cancer treatment [19]].

The surgical treatment of oral cancers can result in a variety of long-term complications, including functional limitations on speech, mastication, and swallowing; neurological problems caused by damage to the cranial nerves; chronic fistulas and healing issues; and aesthetic considerations like severe disfigurement and prosthetic rehabilitation. When these functional and aesthetic impairments are be negatively impacted [19].

There are many serious side effects linked to chemotherapy, including both early and late indicators of chronic toxicity. According to the WHO classification, they can be classified as mild (grade 1), moderate (grade 2), severe (grade 3), or life-threatening or incapacitating (grade 4). Skin and hair, bone marrow and blood, the gastrointestinal tract, and the kidneys can all experience immediate effects. Every organ in the body, including vital organs like the heart, lungs, and brain, may be impacted [20].

4. Pathophysiology of cancer

The majority of solid tumors are similar to healthy tissues in that they require regular oxygen and nutrient delivery, as well as mechanisms for the removal of waste products from cellular metabolism to survive. This function is initially supplied by the host organ's normal blood supply when the tumor first appears. Tumors in compare to healthy tissues, grow larger over time, and eventually the host vascular supply is unable to meet these demands. Tumors will actually form their own functional vascular supply to make up for it [21]. To improve their diffusion, cancer cells override the coagulation

pathway by releasing procoagulant factors, which ultimately activate platelets and inflammatory cells, which in turn promote angiogenesis and the formation of clots. In fact, thrombotic events may reveal an occult malignancy as their initial manifestation [21].
Changes in cells, tissues, and systems that take place during the growth, invasion, and metastasis of cancer make up the complicated pathological process that causes cancer pain. The immune system, peripheral and central nervous systems, and cancer cells interact to cause it [22]. A number of cancers, including breast and colorectal cancer, have obesity as a known risk factor. Carcinogenesis, metastasis formation, and disease progression may be influenced by adipocyte tissue and its microenvironment [23]. The innate immune system coordinates the host response to tumor development, which is similar to inflammation. Through altering each other's functions and abundance, interacting with cancer cells, and adjusting the adaptive immune response, cellular and extracellular components involved in this process influence the growth and progression of tumors. The balance of a complicated and still poorly understood cellular and molecular circuit ultimately determines whether inflammation promotes or inhibits cancer. Inflammation is a versatile process [24].

4.1 Crucial properties characterizing the hostile tumor microenvironment [25]

1. Pathophysiological characteristics showing enhanced level

- Perfusion unadequacies/vascular chaos
- Perfusion heterogeneities
- Permeability of tumor microvessels
- Pressure of intestitial fluids
- Production of lactate
- Production of protons
- Production of adenosine
- Partial pressure of carbon dioxide

2. Pathophysiological characteristics showing reduced level

- Partial pressure of oxygen
- Production of high energy compounds
- Production of extracellular compartments
- Paucity of nutrients
- Paucity of bicarbonate

5. Mechanism of action

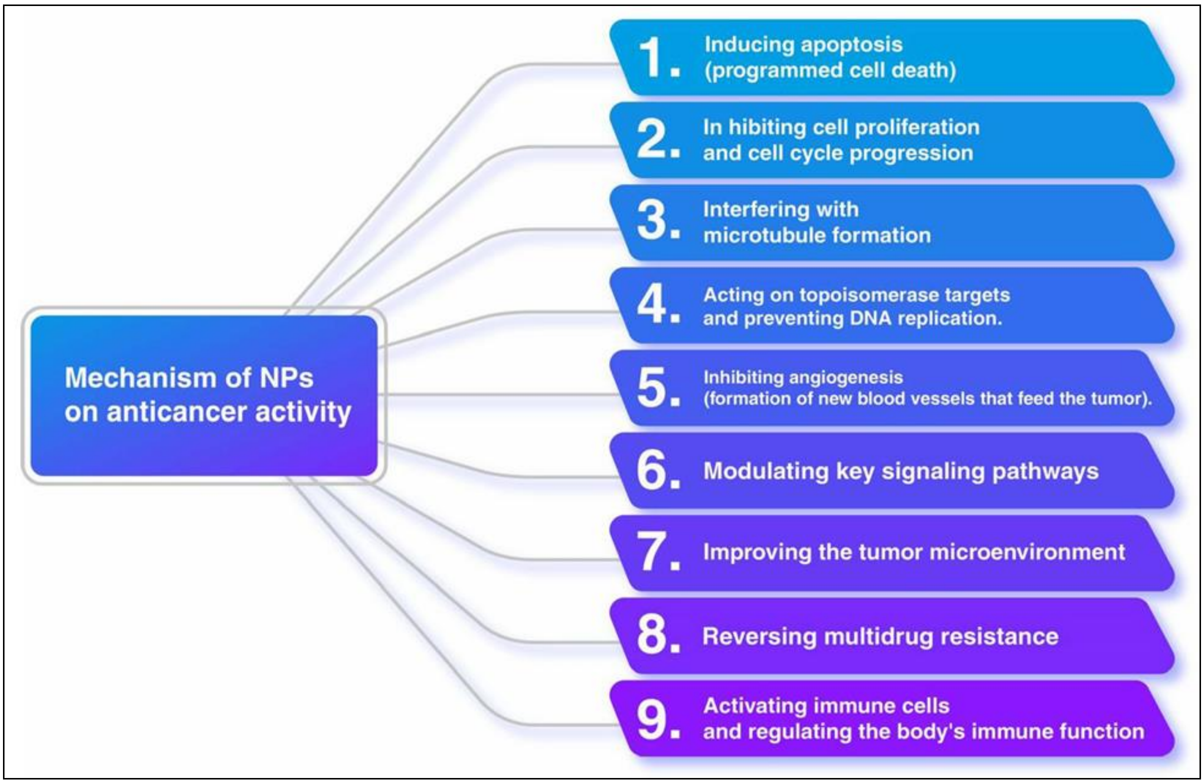

Fig 1: Natural products (NPs) have demonstrated various mechanisms of action in exhibiting anticancer effects [8].

6. Herbal compound with anti-cancer activity [3]

1. Phenolic compounds

- *Curcumin (Diferolelyl methane)*
- *Ginger*
- *Resveratrol*

2. Flavonoid

- *Genistein*
- *Biocalein*
- *Quercetin*

3. Alkaloids

- *7-hydroxystaurosporine (UCN-01)*
- *Vincristine and vinblastine*

4. Lectines

- *Viscum album L.*
- *cytotoxic lectine (KML-C)*

5. Terpenoids

- *Xanthorrhizol*

Almost all fruits and vegetables contain flavonoids, a diverse group of phytonutrients. They are well-known for having antioxidant qualities that aid in shielding cells from harm brought on by free radicals. Certain flavonoids are promising options for cancer prevention and treatment because they have been demonstrated to lower inflammation and stop the growth of cancer cells. Another important class of bioactive substances present in therapeutic plants are alkaloids. They have a variety of pharmacological properties, such as analgesic, anti-malarial, and anti-cancer effects, and are distinguished by their nitrogen-containing structures. Because of their strong anti-cancer effects, some well-known alkaloids, like vincristine and vinblastine, which are extracted from the Madagascar periwinkle, are already utilized in clinical settings. The largest and most varied class of secondary metabolites found in plants are terpenoids, also referred to as isoprenoids. They have a variety of therapeutic uses and are essential to the growth and development of plants. Because terpenoids like *taxol*, which are taken from the bark of the Pacific yew tree, can stop cancer cells from dividing, they are frequently used in cancer chemotherapy. A class of compounds known as polyphenols is distinguished by the presence of several phenol groups. Their anti-inflammatory and antioxidant qualities are well-known. By altering different signaling pathways involved in cell growth and apoptosis, polyphenols like resveratrol, which are present in grapes and red wine, have been investigated for their potential to prevent and treat cancer [8].

7. Herbal remedies for treatment of cancer

Health practices, approaches, knowledge and beliefs incorporating plant, animal, and mineral based medicines, spiritual therapies, manual techniques, applied individually or in combination to treat, diagnose and prevent illnesses and maintain well-being is the definition of traditional medicine given by the World Health Organization (WHO). The most popular traditional medical treatment among the general public and those suffering from chronic illnesses is herbal medicine [26].

It has been shown that vitamins and herbal compounds can cure over 60% of cancers. Due to their superior biological qualities, herbal medicines (HMs) have been used for centuries to treat a wide range of illnesses and relieve pain. Additionally, HMs have demonstrated amazing anticancer properties. HM fractions boost the immune system, trigger apoptosis, control miRNAs, boost the levels of those protective enzymes, activate DNA repair mechanisms, and have antioxidant properties [5]. There is no challenge regarding the use of herbal medicine in cancer, including in various oncology care settings [27]. *Curcumin*, EGCG, *berberine*, *artemisinins*, *ginsenosides*, ursolic acid (UA), silibinin, emodin, triptolide, cucurbitacins, tanshinones, ordonin, shikonin, gambogic acid (GA), artesunate, wogonin, β-elemene, and cepharanthine are among the various natural products derived from Chinese herbal medicine. These products have been found to have emerging anti-cancer properties, including anti-proliferative, pro-apoptotic, anti-metastatic, and anti-angiogenic effects, as well as autophagy regulation, immunity balance, multidrug resistance reversal, and chemotherapy improvement *in vitro* and *in vivo*. These compounds are chosen to be discussed in greater detail because they are regarded as popular and have over 100 supported publications [28]. A number of compounds derived from Chinese herbal medicines have demonstrated anticancer properties that prevent human cancer from developing, proliferating, angiogenesis, and spreading. Specifically, several clinical trials have assessed *berberine*, *curcumin*, and *resveratrol* for the treatment of various cancers [29].

7.1 *Curcumin (turmeric)*

A compound called *curcumin*, which is present in many spices, including turmeric, has been used to treat a number of cancers, including melanoma, colorectal, prostate, stomach, intestine, breast, and ovarian [30]. A compound called *curcumin*, which is present in many spices, including turmeric, has been used to treat a number of cancers, including melanoma, colorectal, prostate, stomach, intestine, breast, and ovarian [30]. Traditional Chinese medicine makes extensive use of *curcumin*, a polyphenol and bioactive metabolite that is extracted from the rhizomes of *Curcuma longa* L. [29].

The Zingiberaceae family is the source of *turmeric* (*Curcuma longa* L.). *Turmeric* was one of the spices used to preserve food in addition to enhancing flavor. The rhizomes of yellow turmeric have a slightly bitter and aromatic flavor. *Turmeric* rhizomes have the ability to scavenge free radicals and are a great source of antioxidants [4]. Out of all the curcuminoids, curcumin has been studied in great detail for a number of ailments, such as cancer, neurological, inflammatory, cardiovascular, and metabolic disorders [11].

To increase efficacy by encouraging apoptosis and overcoming drug resistance, *curcumin* has been investigated in conjunction with chemotherapeutic agents such as paclitaxel. In cancer cells, this substance triggers the extrinsic (death receptor) and intrinsic (mitochondrial) apoptotic pathways [11]. Both *curcumin* and paclitaxel had sequential kinetics of sustained release, and curcumin increased the therapeutic efficacy of paclitaxel by lowering nuclear factor NF-kB [10].

The inhibition of carcinogenesis is one of xanthorrhizol's molecular and cellular mechanisms of anti-cancer action. By adjusting different rates of cancer cell growth and apoptosis, xanthorrhizol indicates its anti-cancer action. DNA fragmentation, cell shrinkage, elongated lamellipodia, and chromatin condensation are typically observed morphologically during apoptosis [31]. While some anti-breast cancer medications have been discovered through research into traditional Chinese medicine (TCM), the mechanisms underlying most of these medications remain unclear. Alkaloids, coumarins, flavonoids, polyphenols, terpenoids, quinone, and artesunate are among the TCM components that have anti-breast cancer properties [32]. However, as far as herbal compounds are considered as drugs, it is erroneously believed that they have no issues in terms of safety and side effects. There are hundreds of species of plants that are toxic to health. In the same way, there are many compounds in otherwise friendly plants that cause cytotoxicity. Based upon testing it has been proved that even anticancer plants result in cytotoxic effects [34].

Fig 2: Dried and broken rhizome of *Curcuma longa* L [32].

7.2 Momordica charantia (MC)

One of the most popular tropical vegetables is *Momordica charantia* (MC), especially in East Africa, South-North Asia, Vietnam, India, China, and Central and South America. Known as bitter gourd or bitter melon, it belongs to the Cucurbitaceae family (Figure 3). In addition to being a vegetable, MC is also believed to be a herbal remedy and a form of folk medicine. The bioactivities of this substance include anti-inflammatory, anti-oxidant, antiviral, anti-cancer, antibacterial, and particularly anti-diabetic properties. The bioactivities of this substance include anti-inflammatory, anti-oxidant, antiviral, anti-cancer, antibacterial, and particularly anti-diabetic properties [35].

Fig 3: morphological characteristic of *Momordica charantia* [35]

7.3 Berberine

The potential of *berberine* in the treatment of vascular diseases has gained more attention in recent years due to the discovery of novel, unique molecular entities derived from herbal medicines that contain this compound [36]. Numerous ailments, including diabetes, cancer, intestinal infections, hypertension, cardiac arrhythmia, congestive heart failure, and hyperlipidemia, have been treated with *berberine* [37]. Active biomolecules like *berberine* have been found in the bark, stem, root, and rhizome of plants like tree turmeric (Berberisaristata), golden thread (Coptis chinesis), barberry (Berberis vulgaris), Oregon grape (Berberis aquifolium), and goldenseal (Hydrastis canadesis). Additionally, *berberine* has been isolated and extracted from a variety of plant genera and families, such as Annickia (Annonaceae), Xanthorhiza (Ranunculaceae), Evodia (Rutaceae), Coelocline (Annonaceae), Argemone (Papaveraceae), Rollinia (Annonaceae), Caulophyllum (Berberi daceae), Zanthoxyllum (Rutaceae), Xylopia (Annonaceae), Bocconia (Papaveraceae), and several others [38]. Among these, *berberine* is widely found in a number of American and Asian species of barberry and goldenseal. *Berberine* treatment reduced TPA-induced VEGF and fibronectin expression in breast cancer cells by inhibiting the PI3K/A pathway [36].

7.4 Resveratrol

A natural polyphenol, *resveratrol* (3, 5, 40-trihydroxystilbene, a phytoalexin) is present in many different plants, including eucalyptus, peanuts, blue berries, cranberries, legumes, rhubarb, grapes, and different types of grass. Despite being found naturally, *resveratrol* can only be extracted in small amounts per kilogram of plant material, such as grape skin [39]. A stilbene found in grapes has been shown to inhibit cell proliferation and induce apoptosis in many cancer cell lines. The bioactive chemicals derived from medicinal plants are great prospects for the development of novel anticancer medications due to their varied chemical structures and mechanisms of action [31].

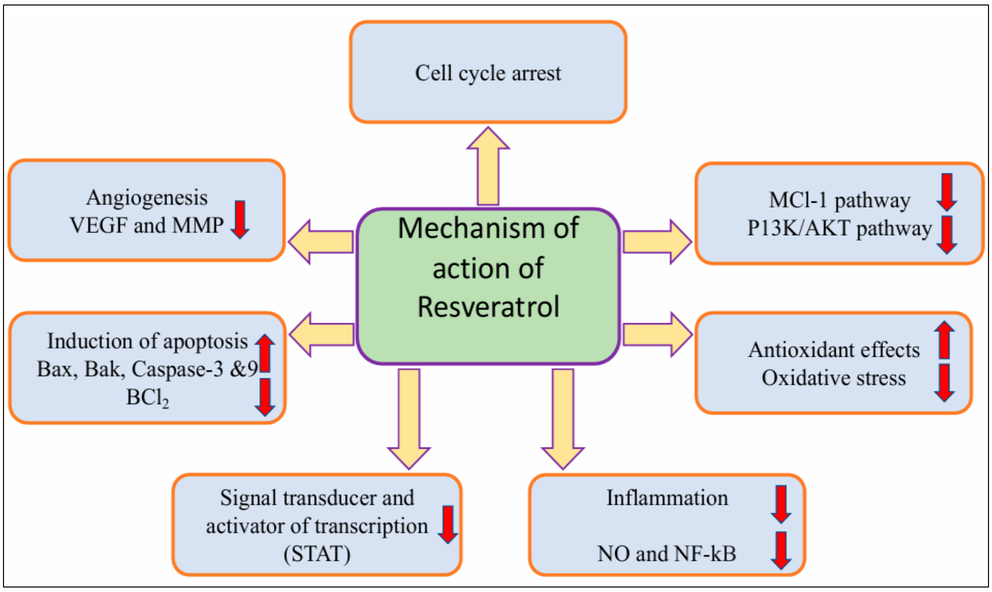

Fig 4: Mechanism of action of *resveratrol* in cancer management through modulating cell signaling pathways [40].

7.5 Garlic

Garlic (Allium sativum L.), a member of the Liliaceae family, is another spice that is frequently consumed. *Garlic* can be eaten raw or cooked, and it can be made into oil or powder. Ancient texts from Egypt, Greece, China, and India mention *garlic* as a traditional medicine as early as 3,000 years ago. In preclinical and epidemiologic studies, *garlic* has been demonstrated to lower the incidence of cancer and heart disease. It has also been proposed as an anti-cancer dietary component [4]. *Garlic's* ability to stimulate immune effector cells, such as T-cells and natural killer cells, is linked to its anti-cancer properties [32]. *Garlic's* primary chemically active component, allicin, has therapeutic properties. Allicin cannot be created by heating *garlic*; it can only be released by crushing or chewing raw *garlic*. Transient thermoreceptors (TRPA1) and transient receptor potential vanilloid 1 (TRRPV1), which contribute to a sensation of heat in raw *garlic*, have a potential channel that is opened by allicin.

Garlic's phytoalexin (allicin), a non-sulfur compound, may help prevent cancer [32].

Fig 5: *Garlic* (*Allium sativum*; Liliaceae family) [32]

7.6 Ginge

Zingiber officinale Roscoe is the botanical name for *ginger*, a member of the Zingiberaceae family. It is a perennial flowering herbaceous plant native to Southeast Asia. Currently produced in Bangladesh, India, China, Nigeria, Nepal, Indonesia, and Japan, it is one of the most popular dietary condiments in the world. The central part of *ginger*, the rhizome, is the horizontal stem from which the roots grow. It can be consumed fresh, dried, pickled, preserved, crystallized, can be dried, powdered, or ground [4]. A number of bioactive substances, such as shogaols, gingerols, zingerone, and paradols, have been found in the rhizome of *ginger* (*Zingiber officinale*), an herb that is frequently used to treat nausea and vomiting [41]. Gingerol, a beta-hydroxy ketone that is 5-hydroxydecan-3-one with a 4-hydroxy-3 methoxyphenyl moiety at position 1, is a component of fresh ginger. Fresh *ginger* is the source of a class of structurally related polyphenolic compounds known as gingerols. The most prevalent bioactive substances found in *ginger* rhizomes as a peppery yellow oil are gingerol and its derivatives (6-gingerol, 8-gingerol, and 10-gingerol) [42]. In ovarian, breast, pancreatic, and colon cancer cells, gingerol is known to exhibit strong anticancer effects. By inhibiting NF-kB and IkB-α phosphorylation, it reduces the expression of TNF-alpha and i-NOS [43].

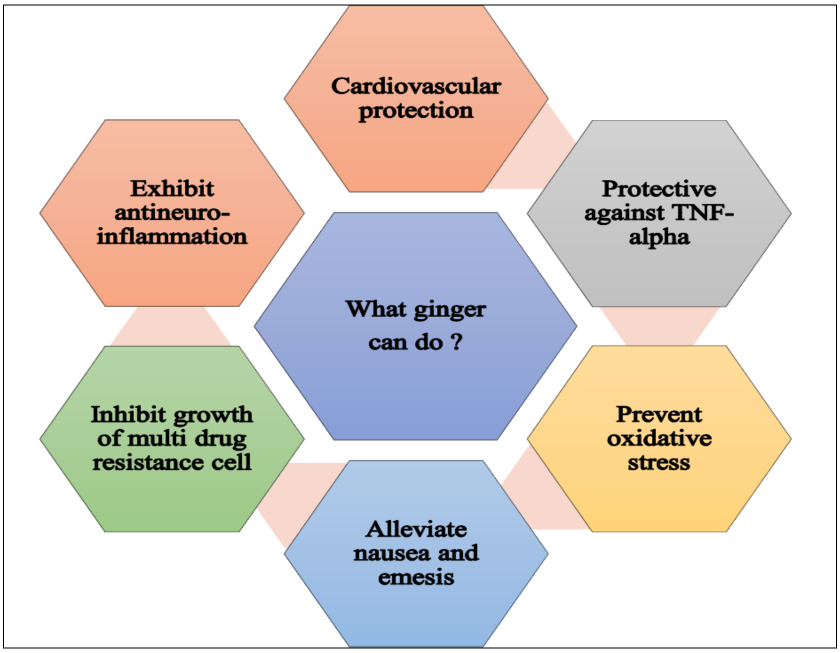

Fig 6: Health benefits and anticancer properties of *ginger* [4].

7.7 Catharanthus roseus

The dried whole plant of *Catharanthus roseus* Linn. *G. Donn*. family Apocynaceae is used to make *Catharanthus roseus*, also known as *Vinca, Catharanthus, Periwinkle, Sada bahar, Sadaphul*, and *Vinca rosea*. It is found in South Africa, India, the United States, Europe, Australia, and the Caribbean Islands [44]. Vinca alkaloids are essential anti-cancer agents. The four main vinca alkaloids used in clinical practice are vindesine (VDS), vinblastine (VBL), vinorelbine (VRL), and vincristine (VCR); only VCR, VBL, and VRL are authorized for use in the United States of America [45]. Vinca alkaloids are agents that are specific to the cell cycle and prevent cells from going through mitosis. Vinca alkaloids selectively attach to b-tubulin and prevent it from forming microtubules through polymerization with a tubulin. Cell division is stopped in metaphase when the mitotic spindle is not intact, preventing duplicate chromosomes from arranging along the division plate. Apoptosis-like alterations occur in cells that are prevented from going through mitosis. They are used to treat testicular cancer, lymphomas, and leukemias [44]. When used alone or in combination, these vinca alkaloids have a wide range of clinically significant anticancer effects. Both malignant and non-malignant cells are affected by vinca alkaloids [46].

Fig 7: *Catharanthus roseus* plant [46]

7.8 Taxols

The bark of *Taxus brevifolia*, a limited resource that produces a very small amount of the compound, is where *taxol* was first isolated. Starting with 10-DAB, which could be derived from a renewable plant resource, a commercially viable semi-synthetic process was used to determine the appropriate amount for therapeutic use. The next challenge, the complicated chemical structure, was not solved until 1971 with the combined help of mass spectrometry, X-ray crystallography, and NMR spectroscopy—an approach that is still relatively new today. *Taxol's* mode of action was described in 1979. It has been discovered that *taxol* binds microtubules and disrupts their dynamics, which leads to the mitotic collapse of cancer cells [47].

8. Conclusion

Herbal medicine offers a valuable adjunct to conventional cancer therapies, providing a rich source of bioactive compounds with anti-cancer properties. The reviewed herbal compounds demonstrate promising therapeutic potential, targeting multiple signaling pathways and modulating cellular processes. Despite certain difficulties and restrictions, there is no denying the advantages of using herbal therapy to treat cancer. By integrating herbal compounds into treatment regimens, healthcare providers can develop more effective and targeted therapies, improving patient outcomes and quality of life. Further research is necessary to fully explore the therapeutic potential of herbal medicine and to develop standardized treatment protocols. As the field continues to evolve, herbal medicine is poised to play an increasingly important role in the fight against cancer. A more comprehensive and efficient method of treating cancer can be achieved by utilizing the possibilities of herbal therapy.

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