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Possible Interventional Anticancer Therapy by Phytomedicines - A Review

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Abstract

Cancer is the rapid proliferation that causes abnormal cells which metastasize to distant tissues. This aberrant signalling mechanism disrupts the regulation of cell proliferation and persistence, ultimately becoming the primary cause of mortality worldwide. The need for novel medications for the treatment and prevention of this deadly disease is constantly rising. Herbal therapies have significance for both preventing and treating a variety of malignancies. Anticancer medications have been discovered and developed from many herbal medicines by the presence of their bioactive phytochemicals such as phenolics, alkaloids, flavonoids, carotenoids, and other secondary metabolites. These herbal products are said to have less toxic side effects when compared to modern treatment strategies. Therapeutic medicinal herbs suppress the progression of cancerous cells by influencing the action of particular enzymes and hormones. The bioactive phytochemicals obstruct cancerous cell multiplication, promote apoptosis of malignant cells, enforce the necrosis of tumors, and inhibit their translocation. They also exert their action by enhancing the number of leukocytes and platelets, promoting the reverse transformation from tumor cells back to usual cells, and they similarly prevent carcinogenesis of regular cells. This review paper enlightens the significance of herbal medicines as anticancer agents and explains, in brief, the mechanism of action and the effects of the herbal bioactive compound. This review helps to explore the potential therapeutic plants as a basis for the discovery of chemotherapy medications.

Keywords*: Anticancer Drugs, Bioactive Phytochemicals, Health and Well-being, Novel Methods, Cancer, Herbal Medicinal Plants.*

Introduction

Cancer

One of the features associated with cancer is the fast proliferation of abnormal cells that multiply beyond usual boundaries, penetrate adjacent anatomical areas, and progress to various parts. The primary cause of death worldwide is unregulated cell division and survival of transformed cells due to a disrupted signaling system [1].

In 2022, India reported 1,461,427 carcinoma cases. Predictions indicate a 12.8% rise in cases by 2025. The comprehensive strategies are crucial for effective cancer control and prevention in India [2].

Natural Products

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Natural products, particularly plants, have been employed for hundreds of years to treat a variety of diseases. These plants have been the source of an astounding number of modern pharmaceuticals. About 2600 BC, the Sumerians and Acadians presented the first reports of the therapeutic properties of herbs [3].

Bioactive constituents of plants have the potential to be extensively employed in conventional treatment, as based on estimates, 80–85% of people worldwide acquire a majority of their medical treatment from traditional drugs [4].

Therapeutic drugs, often used alone or in combination, vary based on factors like location, stage, and the patient's health [5].

Lead components that act as anticancer agents includes alkaloids, terpenoids, steroids, and flavonoids which are referred to as secondary metabolites in medicinal plants. Each of these compounds has unique pharmacological properties [6]. As a result, this article presents a summary of the many therapeutic plants and their main bioactive components that are used to cure cancer [7].

Possible Anticancer Interventions

An effective anticancer medication should destroy cancer cells without significantly harming healthy cells [8].

Programmed cell death is an important phase in the genesis of cancer. By reducing the expression of the Bcl-XL and Bcl-2 genes, lowering reactive oxygen species (ROS), changing the pathway of signalling, activating endonuclease, and raising the expression of the Bax and Bak genes, flavonoids can induce apoptosis [9].

Apoptosis can happen via the intrinsic mitochondrial mechanism or the death receptor-mediated extrinsic mechanism [10]. One of the initial processes in apoptosis via the intrinsic apoptotic pathway is the mitochondria's release of the cytochrome c [11]. Proapoptotic components of the Bcl-2 family, such as Bax and Bak, and antiapoptotic constituents, like Bcl-2 and Bcl-xL, influence the release of cytochrome c. When death receptors bind to the appropriate ligands and start interacting with adaptor proteins, the extrinsic apoptotic pathway is initiated. After then, it merges with the intrinsic route when downstream executioner caspases are activated [10].

The tumor microenvironment is vital for metastasis and angiogenesis. Tumor cells can change the microenvironment [the environment around them] to promote angiogenesis, cell invasion, and inflammation [12].

Regulatory T cells (Tregs) are a genetic variant of T cells, suppresses the defence mechanism to avert excessive immunological responses and autoimmune reactions. Though, the growth of cancer comprises a significant increase in Tregs, which is linked to a worse prognosis for cancer patients and serves as an approach to weakening the immune system's response to tumour cells in the host [13].

Reactive oxygen species (ROS), primarily produced by mitochondrial respiratory chain reactions, serve as essential signalling molecules controlling cell survival and proliferation [14]. However, elevated ROS levels can harm cellular macromolecules, linking to ageing and diseases like cancer [15]. Maintaining proper cellular ROS levels and redox balance is crucial for defending against oxidative stress-induced damage and reducing cancer risk [16].

The majority of cancer types exhibit enhanced NF-κB signaling activity or constitutive activation, which might be crucial for carcinogenesis. Thus, many natural substances and medicinal drugs exhibit the common anticancer mechanism of inhibiting NFκB activity [17]. There are various mechanisms of action of the phytochemicals which are explained in Figure 1 given below.

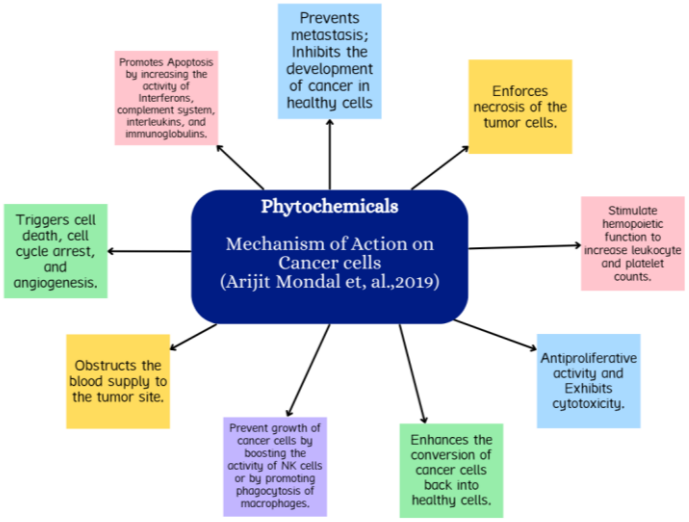

Figure 1. The Mechanism of Phytochemicals on Cancer Cells [18]

Secondary Metabolites

1. **Phenolic compounds**: simple phenols, lignins and lignans, tannins, xanthones, and coumarins [19].
2. **Alkaloids:** Vinblastine, vinorelbine, vincristine, vindesine, castoramine, noranabasamine, amptothecin, helidonine, fagaronine, chelerythrine, lycorine, nitidine chloride, solanine, sanguinarine, evodiamine, piperine, matrine, and tetrandrine [17].
3. **Flavonoids:** Isoflavonoids, flavanones, flavanols, flavonols, flavones and anthocyanidin.
4. **Carotenoids:** β-carotene, B-carotene, canthaxanthin, phytoene, Crocin, Crocetin, Curcumin, Thymoquinon.
5. **Terpenoids:** Artemisinin, taxol, ginsenosides, thymol, limonene, etc.

Table 1. Role of Bioactive Compounds in Anti-cancer Activity

Plant Name	Common Name	Bioactive Component	Action	Treatment	Reference
Cedrous deodara	Himalayan cedar	Isopimpillin, taxifolin, cedeodarin.	Antiproliferative activity	Lung, pancreas, colon, cervix, oral, bladder, and breast cancer.	[20]
Allium sativum	Garlic	Alliin, Diallyl trisulphide	Enhance macrophages activity. Prevents metastasis. Exhibits cytotoxicity.	Lung, bladder, stomach, lung, and breast cancer.	[21]
Ocimum sanctum	Tulsi	Eugenol	Inhibits migration, metastasis,	Choriocarcinoma, lymphosarcoma, lung, and breast	[35]

			angiogenesis, causes cell death and cell cycle arrest.	cancer.	
Catharanthus roseus	Madagascar periwinkle	Vincristine and vinblastine	Arrest mitosis.	Leukaemia, choriocarcinoma, lymphosarcoma, and carcinoma of the lung, breast.	[23]
Ananas comosus	Pineapple	Bromealin	Increases cytotoxicity of monocytes and macrophages, anti-proliferative activity.	Leukaemia.	[33]
Azadirachta indica	Neem	**Azadiractoid:** Azadirachtin and nimbolide	Strengthens host immunological responses, stimulates cell death, inhibition of cancer angiogenesis, and restoration of the cellular reduction/oxidation [redox] balance.	Prostate, Breast, and Oral cancer.	[25]
Aloe barbadensis	Aloe vera	Aloe-emodin and acemannan.	Prevents metastasis, stimulates macrophages.	Colorectal, breast, and cervical cancer.	[39]
Podophyllum peltatum	Mayapple, Devil's apple.	Podophyllin Podophyllotoxin Etoposide and teniposide	Inhibits growth of cancer cells. Interferes with microtubule function during cell division, leading to cell cycle arrest and apoptosis.	Leukaemia, bronchogenic, ovarian and testicular cancers.	[27]

Cannabis sativa	Hemp	Cannabinoids delta-9-tetrahydrocannabinol	Induce apoptosis, Inhibit tumor growth.	Lung, liver, breast, and bladder cancers.	[29]
Zingiber officinale	Ginger	Gingerols, zingerone	Apoptotic induction, prevents the growth of newly formed blood vessels. Suppress and halt the G0/G1 phase, decreases DNA synthesis, and trigger cell death.	Ovarian cancer	[32]
Actinidia chinensis	Kiwi fruit	Rutinum, astragalin, and L-epicatechin	Immunomodulatory and anticancer activities mainly by apoptosis.	Liver, colon, esophagus, and gastric cancer.	[37]
Withania somnifera	Winter cherry, Ashwagandha	Withaferin	Prevents the development and propagation of cancer.	Breast cancer	[40]
Syzygium aromaticum	Clove	Eugenol, anthocyanins.	Control and inhibit the proliferation of malignant cells.	Cancers of the stomach, colon, breast, prostate, melanoma, and leukaemia.	[35]

Cedrus deodara

Cedrus deodara, commonly known as Himalayan cedar, is native to the Western Himalayas and found in Pakistan, China, Korea, and other parts of India. Rich in terpenoids and flavonoids, its bioactive constituents include isopimpillin, lignans, taxifolin, and cedeodarin. The hydro-alcoholic extract of *C. deodara* has demonstrated anti-proliferative properties across 14 human cancer cell lines, spanning various tissues like pancreas, colon, cervix, oral cavity, bladder, breast, and lung [20] as described in Table 1.

Allium sativum

Allium sativum, known as garlic, contains organosulfur compounds (OSCs) with chemo-preventive properties. Functioning as a potent anticancer agent, garlic induces apoptosis, controls cell cycle progression, and alters signal transduction pathways. It also regulates nuclear variables linked to inflammation and the immune system [21]. Components isolated

from garlic suppress cancer initiation and development. Dialyl disulfides (DADS) specifically influence the viability and proliferation of certain cancer cells, inducing apoptosis through the mitochondrial pathway and causing cell cycle arrest in the G2/M phase [22].

Catharanthus roseus

Catharanthus roseus, known as Madagascar periwinkle contains Vincristine sulfate is effective in treating lymphocytic and acute leukemia in children by preventing cancer cells from entering their mitotic phase [23]. Vinblastine sulfate is used in the treatment of choriocarcinoma, lymphosarcoma, lung, breast, and other organ carcinomas, inhibiting microtubule synthesis in cancer cells and demonstrating anticancer effectiveness [24].

Azadirachta indica

Neem, or *Azadirachta indica*, contains polyphenols like quercetin and β-sitosterol in fresh leaves in which Quercetin demonstrates antimetastatic functions by inhibiting tumor cell attachment, migration, and invasion [25]. Nimbolide, found in neem, triggers cell death by cleaving pro-caspase-3, pro-caspase-8, and PARP and altering IGF signaling molecules [26].

Podophyllum hexandrum

Podophyllum hexandrum, an endangered medicinal plant, contains anticancer compounds such as alpha and beta peltatin and podophyllotoxin. They are utilized in the treatment of skin malignancies [27]. Despite being included in clinical investigations; their use was withdrawn due to unacceptable hazardous effects and inadequate effectiveness [28].

Cannabis sativa

Cannabis sativa, commonly known as hemp, contains cannabinoids (CB), an active component responsible for its therapeutic effectiveness [29]. CB derivatives have been shown to inhibit cell division and survival in various cancers by selectively targeting and eliminating tumors. They disrupt cellular processes and signaling pathways, leading to cell death, growth inhibition, and prevention of migration. Additionally, cannabinoids may indirectly influence the immune system, tumor microenvironment, and prevention of vascularization [30].

Zingiber officinale

Zingiber officinale, commonly known as ginger, has been utilized both as a food ingredient and medicinally for various human illnesses [31]. Its bioactive component, [6]-gingerol, along with EG, demonstrates antiproliferative, anticancer, and anti-invasive properties through pathways such as NF-κB, STAT3, Rb, MAPK, PI3K, Akt, ERK, cIAP1, cyclin A, cyclin-dependent kinase (Cdk), cathepsin D, and caspase-3/7 in experimental (in vitro/in vivo) and medical trials [32].

Ananas comosus

Ananas comosus, commonly known as pineapple, contains bromelain and peroxidase. The combined action of peroxidase and bromelain has shown significant potential in leukemic K562 cells with no toxicity [33]. A. comosus leaf extract has demonstrated the ability to lower protein denaturation and regulate the release of prostaglandins, interleukin-1beta, and tumor necrosis factor-alpha in activated macrophages generating reactive oxygen species [34].

Syzygium aromaticum

Clove (*Syzygium aromaticum*) is highly esteemed in traditional medicine, with its bioactive component eugenol exhibiting anticancer effects - inducing programmed cell death, cell cycle arrest, and inhibiting angiogenesis, migration, metastasis, and proliferation on various cell lines. Eugenol, when used as an adjuvant therapy with conventional chemotherapy, can reduce toxicity and enhance effectiveness [35].

Apoptosis occurs due to lowering inflammatory cytokine levels, reducing prostaglandin production, inhibiting cyclooxygenase-2 activity, triggering S phase cell cycle arrest, and blocking NF-κB activation [36].

Actinidia chinensis

Actinidia chinensis Planch (ACP), commonly known as kiwifruit, contains astragalin, a crucial component that may inhibit Bcl-2 expression, increase Bax expression, cleave caspase 3, 8, and 9, and regulate the apoptosis signaling pathway. This suggests a potential role in preventing the progression of liver tumor cells and treating liver malignancy [37]. Kiwi extracts have been observed to significantly decrease the proliferation of human oral gingival fibroblasts (HGF) and human squamous cell carcinoma (HSC-2) [38].

Conclusion and Future Aspect

Cancer, a leading global cause of death, is expected to rise due to lifestyle changes and industrialization. Medicinal plants, vital for human health, are screened for bioactive anticancer components. Standardizing their doses is essential for effective tumor treatment. This review concludes that herbal medicinal plants and their derivatives can effectively treat various cancers, highlighting their antitumor action and diverse biological properties. In-vitro studies and diverse clinical trials are vital to understand the mechanisms and ensure efficacy of plant-derived anticancer drugs. This paper assists future researchers in exploring herbs - applications, toxicity, and clinical trials. The pharmaceutical industry hopefully speeds up the development of powerful commercial medications, offering advanced options for cancer treatment and benefiting humanity.

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Conflict of Interest

There exist no conflicts of interest, as stated by the authors.

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