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Phytochemicals in Cancer Treatment: A Review

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ABSTRACT

Cancer is a heterogeneous disease characterized by uncontrolled proliferation and impaired cell cycle leading to the growth of abnormal cells that invade and metastasize to other parts of the body. Oxidative stress, hypoxia, genetic mutations and lack of apoptotic function are the main internal causes of cancer, whereas the external causes are related to increased exposure to stress, pollution, smoking, radiation and ultraviolet rays. Phytochemicals derived from plants, serve as vital resources for novel drugs and are also sources for cancer therapy. The objective of this review is to describe the active compounds derived from the natural products/plants, along with their pharmacologic action and molecular targets.

Keywords: Phytochemicals, anti-cancer drugs, mechanism, natural products, flavonoids

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1. INTRODUCTION

Cancer is a serious threat and mortality of cancer are high in global[1,2]. In addition to causing serious harm to the patient's body, cancer also imposes a huge economic burden on patients, and the burden on developing countries is growing[3]. Traditionally, treatment for cancer uses the four methods of surgery, radiotherapy, chemotherapy, and immunotherapy alone or in combination[4]. Accompanied by the use of chemotherapy drugs, drug resistance caused by cancer cells adapting to chemotherapeutic agents is the main reason for obstructing the efficacy of chemotherapy drugs[5]. Therefore, the development of adjuvant or alternative drugs is necessary. Biologically active phytochemicals present in plants and natural products, improve treatment efficiency in cancer patients and decrease adverse reactions. These phytochemicals having significant antitumor potential[6] .In the present review, an attempt has been made to collect information about the anti-cancer phytochemicals that are evaluated at preclinical and clinical levels.

2. PHYTOCHEMICALS USED IN CURRENT CANCER TREATMENT

Scientific evidences indicate that phytochemicals have significant antitumor potential. Approximately, 50% of approved anticancer drugs originate from natural products[7,6]. These phytochemicals have been tested for anti-cancer efficacy at both *in vitro* and *in vivo* levels. They possess complementary and overlapping mechanisms to slow down the carcinogenic process by scavenging free radicals[8], suppressing survival and proliferation of malignant cells[9], as well as diminishing invasiveness and angiogenesis of tumors[10]. They exert wide and complex range of actions on different molecular targets and signal transduction pathways including membrane receptors[11], kinases[12], downstream tumor-activator or -suppressor proteins[13], transcriptional factors[14], microRNAs (miRNAs)[15], cyclins, and caspases[9].

The four major classes of clinically used plant-derived anticancer compounds include vinca alkaloids, taxane diterpenoids, camptothecin derivatives, and epipodophyllotoxin (Table 1). Apart from these phytochemical classes, other plant-derived anticancer agents from different classes such as combretastatins, homoharringtonine (omacetaxine mepesuccinate, cephalotaxine alkaloid), and ingenol mebutate are also used (Table 1).

Table 1: Phytochemicals used in current cancer treatment

Phytochemicals	Pharmacological action	Type of cancer	Ref
Vinca alkaloids Vinblastine, Vincristine, Vindesine , Vinflunine, Vinorelbine	Inhibit microtubule polymerization and assembly, leading to metaphase arrest and cell death.	Non-small-cell lung carcinoma (NSCLC), breast, lung, leukemia, Hodgkin and non-Hodgkin lymphomas, testicular carcinoma, Kaposi's sarcoma, and second-line transitional cell carcinoma of the urothelium (TCCU)	16
Taxanes Cabazitaxel, Docetaxel, Paclitaxel	Inhibit microtubule function resulting in cell cycle arrest and aberrant mitosis.	NSCLC, head and neck, breast, prostate, gastric adenocarcinoma	17,18
Podophyllotoxin Etoposide, Teniposide	Inhibits DNA synthesis by forming a complex with topoisomerase II and DNA.	Osteosarcoma, NSCLC cervical, nasopharyngeal, colon, breast, prostate, and testicular cancer	19
Camptothecin Irinotecan , Topotecan	Stabilizes topoisomerase I-DNA complex thereby preventing religation of single strand breaks resulting in lethal double-stranded breaks in DNA.	Ovarian, cervical, colorectal, and small cell lung cancer (SCLC)	20
Combretastatin A4	Inhibits polymerization of tubulin causing disruption of the tumor endothelial cells lining the tumor vasculature	Polypoidal choroidal vasculopathy, anaplastic thyroid cancers	21
Homoharringtonine	Binds to large ribosomal subunit, which affects chain elongation and prevents protein synthesis	Chronic myeloid leukemia	22
Ingenol mebutat	It induces rapid induction of cell death in the treated area and it activates inflammatory response, capable of eliminating the residual cells	Actinic keratosis	23
Homoharringtonine (HHT)	HHT binds to the A-site cleft in the large ribosomal subunit, which affects chain elongation and prevents protein synthesis.	Chronic myeloid leukemia	24
Combretastatins compounds Combretastatin A1 , Combretastatin A4 , Combretastatin A4 phosphate (CA4P)	These compounds indirectly act on cancer cells by inhibiting tubulin polymerization causing disruption of the tumor endothelial cells lining the tumor vasculature, inducing rapid vascular collapse in solid tumors	Thyroid and ovarian cancer.	21
Resveratrol (stilbenoid)	Delayed the development of recurrence by lengthening the prostate specific antigen doubling time (PSADT)	Low-grade GI neuroendocrine tumors	25
Paclitaxel (tricyclic diterpenoid)	Effectiveness on both solid and disseminated tumors and a broad spectrum of antitumor activity predicted by its unique mechanism of action, which targets the very basic elements of the cancer phenotype like cell proliferation	breast, ovarian and lung cancers	26

3. PHYTOCHEMICALS USED AS CANCER CHEMOPREVENTIVE AND TREATMENT AGENTS

Various review articles summarized natural phytochemicals and their anti-cancer effects, such as Vitamin E from plant oil[27] boron-rich natural compound[28] , hydroxytyrosol from virgin olive oil[29] , resveratrol from grapes[30], phytoestrogens most notably from soybean[31], or EGCG from green tea polyphenols[32]. Abundant evidence has been collected on preclinical efficacy of number of phytochemicals in various animal models which is summarized in Table 2 and Fig.1.

Table 2: Phytochemicals used in cancer therapy

Phytochemicals	Source	Pharmacological action	Types of Cancer	Ref
Allicin (organosulfurs)	Garlic (*Allium sativum*)	STAT3 signaling pathway	Lung adenocarcinoma A549 and H1299 cells	33,34
Andrographolide (diterpenoid)	Green chireta (*Andrographis paniculata*)	HIF-1a, VEGF, and PI3K pathway	HT-29 cells	35
Apigenin (flavonoid)	Parsley (*Petroselinum crispum*)	Intrinsic apoptosis pathway	Human chondrosarcoma Sw1353 cells	36,9
Baicalein (flavonoid)	Baikal skullcap (*Scutellaria baicalensis*)	MAPK, ERK, and p38 signaling pathways	Human colon cancer HCT116 cells	12,37
Curcumin (phytopolyphenol)	Turmeric (*Curcuma longa*)	Modulates cell signaling and gene expression regulatory pathways	Human A375 melanoma cells	38
Dicumarol	Yellow sweet clover (*Melilotus officinalis*)	Intrinsic apoptosis pathway	DIC as a potential anticancer agent when female fertility preservation is a concern	14,39
Epigallocatechin (flavonoids)	Green tea (*Camellia sinensis)*	Inhibit cell proliferation and apoptosis	Human breast cancer MDA-MB-231 cells	40
Emodin - Resin(anthraquinone derivative)	Root and rhizome of *Rheum palmatum* L.	PI3K/AKT and MAPK signaling pathways	Human hepatocellular cancer SMMC-7721 cells	41,42
Genistein (isoflavonoid)	Soya beans (Glycine max (legumes)	WNT/b-catenin and Akt signaling pathway	Human leukemia cell line HL-60	43
Gingerol (polyphenol)	Rhizomes of ginger (Zingiber officinale)	Intrinsic apoptosis pathway	Inhibition of lung-metastatic, MDA-MB-231 human breast cancer cell proliferation	44,45
Glycyrrhizin (triterpenes)	Roots of licorice (Glycyrrhiza glabra)	TxA2 and JAK/STAT signaling pathway	Human lung adenocarcinoma A549 cells	46
Hispidulin (flavone)	Roseleaf sage (*Salvia involucrate*)	Intrinsic apoptosis pathway	Inhibited the Caki-2 (human clear cell renal cell carcinoma) tumor growth, Human hepatocellular carcinoma Bel7402 cell	47,48
Licochalcone A (chalcone)	Roots of Liquorice (*Glycyrrhiza glabra*)	Cyclins and CDKs	Human cervical cancer cell SiHa	10
Nimbolide (triterpene)	Neem (Azadirachta indica)	PI3K/AKT/mTOR and ERK signaling	Pancreatic cancer HPAC cell	49
Pterostilbene (polyphenol)	Grapes (*Vitis vinifera, Vitaceae*)	Mitochondrial mediated apoptosis; ERK and STAT3 signaling	Inhibited EC109 tumor growth	50
Sulforaphane (organosulfur)	Cabbage (*Brassica oleracea*)	Cell cycle arrest and apoptosis. Targets: caspase 8, p21, hsp90	Barrett esophageal adenocarcinoma (BEAC) cells	51
Thymol (monoterpenoids)	Thyme (*Thymus vulgaris*) and Oregano (*Origanum vulgare*)	Mitochondrial mediated apoptosis	Oral squamous cell carcinoma Cal27- and HeLa-	52
Thymoquinone (quinone)	Black cumin seed oil (*Nigella sativa*)	STAT3 and associated protein	Human gastric cancer cells, breast cancer EMT6/P cell line	53
Ursolic acid (triterpenoids)	Snake-needle grass *(Oldenlandia diffusa)*	Ki-67, CD31, and miR-29a	Cervical cancer cell	54
Withaferin-A (phytosterols)	Ashwagandha *(Withania somnifera)*	AKT signaling FOX03a-Par-4 cell death pathway, ERK, and p38 pathway	Human colorectal carcinoma (HCT-116) cells	55

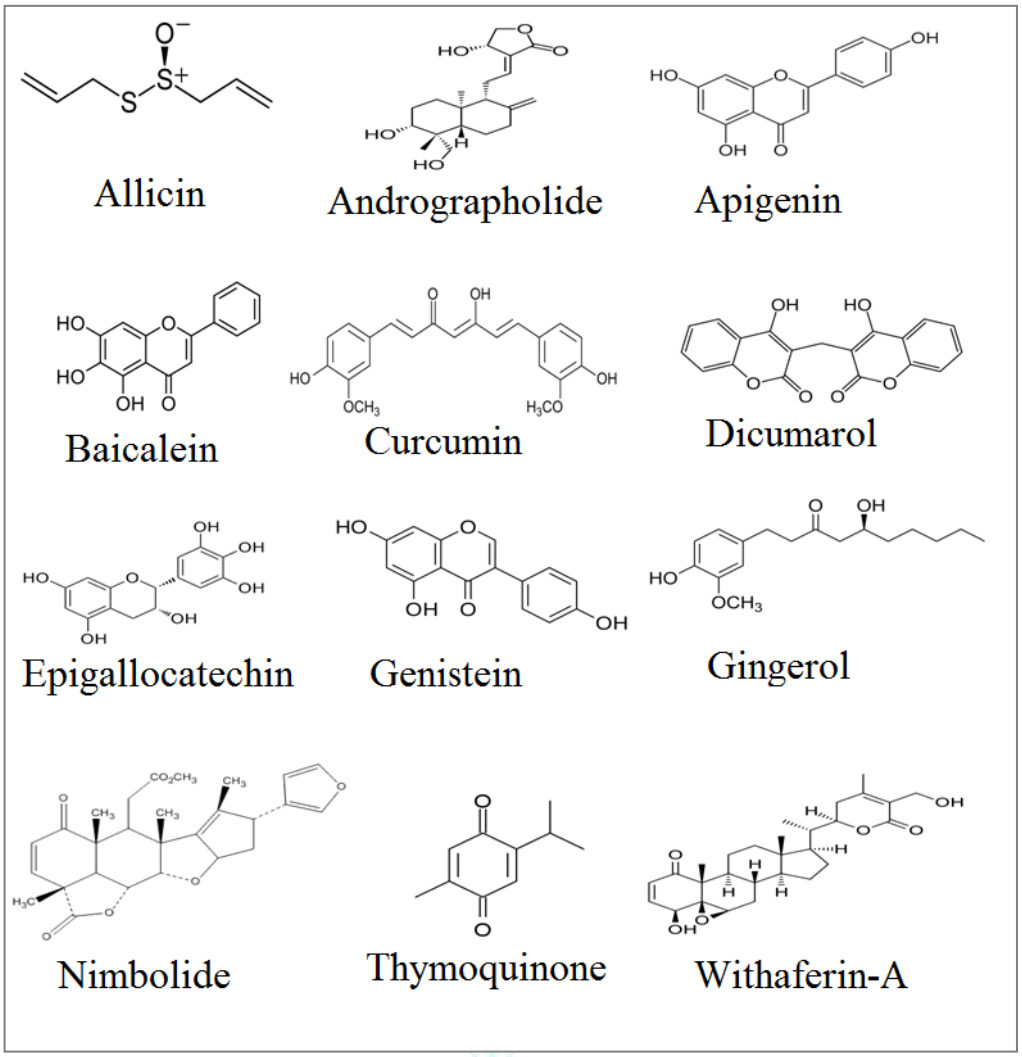

Fig.1: Chemical structures of some anticancer phytochemicals

4. FLAVONOIDS AS ANTICANCER AGENTS

Flavonoids are polyphenolic compounds subdivided into 6 groups: isoflavonoids, flavanones, flavanols, flavonols, flavones and anthocyanidins found in a variety of plants. Fruits, vegetables, plant-derived beverages such as green tea, wine and cocoa-based products are the main dietary sources of flavonoids. Flavonoids have been shown to possess a wide variety of anticancer effects: they modulate reactive oxygen species (ROS)-scavenging enzyme activities, participate in arresting the cell cycle, induce apoptosis, autophagy, and suppress cancer cell proliferation and invasiveness. Flavonoids have dual action regarding ROS homeostasis—they act as antioxidants under normal conditions and are potent pro-oxidants in cancer cells triggering the apoptotic pathways and down regulating pro-inflammatory signaling pathways[56]. Flavonoids exert a wide variety of anticancer effects: they modulate ROS-scavenging enzyme activities, participate in arresting the cell cycle, induce apoptosis, autophagy, and suppress cancer cell proliferation and invasiveness[57, 58]. Isoflavone genistein promoted breast cancer cell arrest at G2/M phase and subsequent ROS dependent apoptosis[59]. Daidzein promoted apoptosis in breast cancer MCF-7 cells due to the ROS generation[60]. Flavanone hesperetin induced apoptosis of gall bladder carcinoma[61], esophageal cancer[5], hepatocellular carcinoma and human breast carcinoma MCF-7 cells[62] via activating the mitochondrial apoptotic pathway by increasing the ROS production. Flavanone naringenin exerted anti-cancer effects on choriocarcinoma JAR and JEG 3 cell lines by inducing the generation of ROS and activation of signaling pathways[63]. Cocoa catechins and procyanidins have been shown to induce apoptotic morphological changes, DNA damage and apoptosis in epithelial ovarian cancer cells due to their prooxidant properties[64]. Cocoa polyphenolic extract activated the ERK1/2 pathway, thus increasing the activities of glutathione peroxidase and reductase in HepG2 cells. Flavonol quercetin exerted potent cancer chemopreventive properties. Recent studies showed that quercetin reduced the proliferation of hepatocellular carcinoma HepG2 cells decreasing the intracellular ROS level[65]. Flavonol kaempferol exerted cytotoxic effects on rat hepatocellular carcinoma cells via ROS-mediated mitochondrial targeting[66]. The anticancer activities of flavones apigenin and luteolin in ovarian cancer cell lines (A2780, OVCAR-3 and SKOV-3) were also related to the changes in ROS signaling, as well as to the promotion of apoptosis[67]. Flavone chrysin was reported to augment ROS and lipid peroxidation levels, leading to the death of choriocarcinoma (JAR and JEG3), bladder cancer and ovarian cancer (ES2 and OV90) cells[68]. Thus, numerous studies show beneficial effects of flavonoids as potent antioxidants under normal and pro-oxidants under pathological conditions, capable of activating apoptosis and suppressing proliferation and inflammation.

5. CONCLUSION

Cancer is a highly malignant disease. Based on its current status, it is urgent to explore a kind of drug with lower toxicity, lower side effects and effective drug for cancer treatment or adjuvant therapy. The tumor occurrence and development involve multiple links, multiple pathways, and multiple targets. The complexity of the interaction between the various links may lead to clinical reactions such as limited therapeutic effect and large side effects. In this review, an attempt has been made to provide information of phytochemicals that are used in cancer treatment. This information will be extremely useful to identify a series of additional plant-derived drugs to treat cancer with minimum side effects.

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The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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