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A Review On Medicinal Plants Having Anticancer Activity

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ABSTRACT

The rising burden of cancer worldwide calls for an alternative treatment solution. Herbal medicine provides a very feasible alternative to western medicine against cancer. This article reviews the selected plant species with active phytochemicals, the animal models used for these studies, and their regulatory aspects. This study is based on a meticulous literature review conducted through the search of relevant keywords in databases, Web of Science, Scopus, PubMed, and Google Scholar. Twenty plants were selected based on defined selection criteria for their potent anticancer compounds. The detailed analysis of the research studies revealed that plants play an indispensable role in fighting different cancers such as breast, stomach, oral, colon, lung, hepatic, cervical, and blood cancer cell lines. The in vitro studies showed cancer cell inhibition through DNA damage and activation of apoptosis-inducing enzymes by the secondary metabolites in the plant extracts. Studies that reported in vivo activities of these plants showed remarkable results in the inhibition of cancer in animal models. Further studies should be performed on exploring more plants, their active compounds, and the mechanism of anticancer actions for use as standard herbal medicine.

Keywords: cancer, apoptosis, herbs, cell lines, in vivo

INTRODUCTION

Cancer is a chronic disease and one of the main causes of death around the world. The global cancer burden is extensively rising, and it is considered as the second cause of death after cardiovascular disease. In 2020, 19.3 million new cancer cases were estimated, with 10.0 million cancer deaths worldwide and 250 million disability-adjusted life years because of cancer . Regardless of the new developments in cancer therapy and revolutionary advances in genomics and molecular biology, multidrug resistance and drug side effects are still the vital cause of cancer treatment failure. Since plants are a rich source of natural compounds that are characterized by their therapeutic effects, studying these compounds is thought to be a promising line for research on cancer. In this context, phytochemicals, secondary metabolites extracted from plants, have diverse applications, including antidiabetic, anti-inflammatory, cardiovascular protective, antioxidant, and anticancer effects .In particular, these phytochemicals can be classified into different groups such as flavonoids, alkaloids, phytosterols, terpenoids, sulfides, polyphenols, and others, which have been considered an important reservoir for novel anticancer agents. Hence, plant secondary metabolites are recognized with many properties such as tumor growth inhibition,apoptosis induction, immune modulation, and angiogenesis suppression. As well,several epidemiological studies have reported the role of phytochemicals and their derived analogues in modulating tumor cell-activating proteins, enzymes, and signaling pathways, stimulating DNA repair mechanisms, and conquering free radicals production. They also interact with many intracellular pathways that regulate cell growth, such as the STAT3, PI3K/Akt/NF-κB signaling pathway, mTOR, and the Bcl-2/Bax mitochondrial pathway.

In this review, we have tried to choose the most effective and well-known phytochemical's that display a distinctive anticancer activity. As well, we described these phytochemicals thoroughly, starting with their chemical structure and ending with their antitumor activity.

MECHANISM OF CANCER THERAPY

1. Inhibiting cancer cell proliferation directly by stimulating macrophage phagocytosis and enhancing natural killer cell activity.

2. Promoting apoptosis of cancer cells by the increase of production of interferon, interleukin-2 immunoglobulin and complement in blood serum.

3. By enhancing the number of leukocytes and platelets by stimulating the hemopoietic function.

4. By enforcing the necrosis of tumor and inhibiting its translocation and spread by the blockage of blood source of tumor tissue.

5. Promoting reverse transformation of tumor cells into normal cells.

Fig 1: Mechanism of Cancer Therapy

ANTICANCER DRUGS

1) Mechlorethamine (Mustine HCl)-

It is the first nitrogen mustard; highly reactive and local vesicant—can be given only by i.v. route. It produces many acute effects like nausea, vomiting and haemodynamic changes. Extravasation during i.v. injection may cause sloughing. Hodgkin and non-Hodgkin lymphomas are the main indications. It has been a component of erstwhile MOPP regimen.

Dose: 0.1 mg/kg i.v. daily × 4 days; courses may be repeated at suitable intervals.

MUSTINE 10 mg dry powder in vial.

2) Methotrexate (Mtx)

This folic acid analogue is one of the oldest and highly efficacious antineoplastic drugs which acts by inhibiting dihydrofolate reductase (DHFRase)—blocking the conversion of dihydrofolic acid (DHFA) to tetrahydrofolic acid (THFA). Utilizing the folate carrier it enters into cells and is transformed to more active polyglutamate form by the enzyme folypolyglutamate synthase (FPGS). Tetrahydrofolic acid is an essential coenzyme required for one carbon transfer reactions in de novo purine synthesis and amino acid interconversions. The inhibition is pseudoirreversible because Mtx has 50,000 times higher affinity for the enzyme than the normal substrate.Methotrexate has cell cycle specific action kills cells in S phase; In addition to DHFRase it inhibits thymidylate synthase as well so that DNA synthesis is primarily affected. However, synthesis of RNA and protein also suffers. It exerts major toxicity on bone marrow—low doses given repeatedly cause megaloblastic anaemia, but high doses produce pancytopenia. Mucositis and diarrhoea are common side effects. Desquamation and bleeding may occur in g.i.t. Methotrexate is absorbed orally, 50% plasma protein bound, little metabolized and largely excreted unchanged in urine. Salicylates, sulfonamides, dicumerol displace it from protein binding sites. Aspirin and sulfonamides enhance toxicity of Mtx by decreasing its renal tubular secretion. The toxicity of Mtx cannot be overcome by folic acid, because it will not be converted to the active coenzyme form. However, Folinic acid (N5 formyl THFA, cirtrovorum factor) rapidly reverses the effects. Thymidine also counteracts Mtx toxicity.Methotrexate is apparently curative in choriocarcinoma: 15–30 mg/day for 5 days orally or 20–40 mg/m2 BSA i.m. or i.v. twice weekly.

NEOTREXATE 2.5 mg tab, 50 mg/2 ml inj; BIOTREXATE 2.5 mg tab, 5, 15, 50 mg/vial inj.

3) Fluorouracil (5-FU)

It is converted in the body to the corresponding nucleotide 5-fluoro-2-deoxyuridine monophosphate, which forms a covalent ternary complex with methyl-THFA and tymidylate synthase (TS) resulting in irreversible inhibition of TS. Consequently conversion of deoxyuridilic acid to deoxythymidylic acid is blocked. Selective failure of DNA synthesis occurs due to non-availability of thymidylate. Accordingly, thymidine can partially reverse 5-FU toxicity. 5-FU itself gets incorporated into RNA, interferes with RNA synthesis and function contributing to its cytotoxicity. Even resting cells are affected, though rapidly multiplying ones are more susceptible. Since inhibition of TS by 5-FU is dependents on the presence of THFA, concurrent infusion of leucovorin enhances the efficacy of 5-FU. Cisplatin and oxaliplatin also synergise with 5-FU. Most protocols now employ 5-FU along with leucovorin and cisplatin/ oxaliplatin. Currently, 5-FU is a commonly used anticancer drug for many solid malignancies, especially of colon, rectum, stomach, pancreas, liver, urinary bladder, head and neck. Oral absorption of 5-FU is unreliable. It is primarily used by i.v. infusion. 5-FU is rapidly metabolized by dihydropyrimidine dehydrogenase (DPD) resulting in plasma t½ of 15–20 min after i.v. infusion. Genetic deficiency of DPD predisposes to severe 5-FU toxicity. Major toxicity of 5-FU is exerted on

the bone marrow and g.i.t. causing myelosuppression, mucositis, diarrhoea, nausea and vomiting.Peripheral neuropathy (hand-foot syndrome) also occurs.

Dose: 500 mg/m2 i.v. infusion over 1–3 hours weekly for 6–8weeks, or 12 mg/kg/day i.v. for 4 days followed by 6 mg/kg i.v. on alternate days, 3–4 doses.

FLURACIL, FIVE FLURO, FIVOCIL 250 mg/5 ml and 500 mg/10 ml vial.

4) Cisplatin

It is hydrolysed intracellularly to produce a highly reactive moiety which causes cross linking of DNA. The favoured site is N7 of guanine residue. It can also react with –SH groups of cytoplasmic and nuclear proteins. Effects resemble those of alkylating agents and radiation.It is bound to plasma proteins, penetrates tissues and is slowly excreted unchanged in urine with a t½ of about 72 hrs. Negligible amounts enter brain. A copper transporter CTR1 is involved in the entry of platinum complexes into the tumour cells. The same are extruded from the cells by the transporter MRP1 as well as by copper efflux proteins. Resistance to cisplatin can be imparted by variation in the levels of these proteins.Cisplatin is very effective in metastatic testicular and ovarian carcinoma. It is widely used in many other solid tumours like lung, bladder, esophageal, gastric, hepatic, head and neck carcinomas. Cisplatin is administered by slow i.v. infusion 50–100mg/m2 BSA every 3–4 weeks;

CISPLATIN, CISPLAT, PLATINEX 10 mg/10 ml, 50 mg/50 ml vial.

PLANT DERIVED NATURAL PRODUCT HAVING POTENTIAL ANTICANCER EFFECT

1) Curcumin

Fig 2: Curcumin

Scientific Name: Curcuma Longa

Common Name : Turmeric

Morphology Of Plant

Colour: Yellow

Odour: Warm

Taste: Bitter, almost musky

Family: Zingiberaceae

Kingdom: Plantae

Species: C. longa

Genus: Curcuma

Part of Use: Rhizome

Chemical Constituents:

The major compounds were ar-turmerone (20.50 %), β-sesquiphellandrene (5.20 %) and curcumenol (5.11 %). Curcumin was identified using IR, 1H and 13C NMR.

Extraction Process:

Curcumin from plant materials is obtained using several methodologies, from traditional extraction processes, like Soxhlet extraction, maceration, and solvent extraction to recent extraction technologies, such as extraction by means of ultrasound, microwaves, enzymes, and supercritical liquids. The isolation and purification of curcumin from crude extracts is accomplished by techniques such as column chromatography, high-performance liquid chromatography (HPLC), high-speed counter-current chromatography, supercritical fluid chromatography, either alone or in combination.

Uses:

Curcumin has shown very promising results in suppressing cancer cell growth and proliferation in several different types of cancer, such as prostate, colorectal, breast, pancreatic, brain, head, and neck cancers.

2. Ginkgo biloba

Fig 3 : Ginkgo Biloba

Scientific Name : Ginko Biloba

Common Name: Maidenhair Tree

Family : Ginkgoaceae

Kingdom : Plantae

Genus : Non flowering seed plant

Colour: Dull-grey-green to yellow green

Odour: Rotten butter

Taste: Sweet / Slightly bitter

Part Of use: Leaves and seeds

Chemical Constituents:

Important constituents present in the medicinally used leaves are the terpene trilactones, i.e., ginkgolides A, B, C, J and bilobalide, many flavonol glycosides, biflavones, proanthocyanidins, alkylphenols, simple phenolic acids, 6-hydroxykynurenic acid, 4-O-methylpyridoxine and polyprenols.

Extraction Process:

Twice 800g of ground green leaves of Ginkgo biloba are extracted in countercurrent fashion with twice 13.5 liters of an acetone/water (70:30) mixture. This first extraction is performed at a temperature of between approximately 50 and 60° C. A temperature of approxi mately 55 C. has been used quite satisfactorily in practice. After separation of the residuum by filtration, the liquors are concentrated under reduced pressure to a volume of approximately 1.9 liters, and a separation of the precipitate is then performed by decantation followed by filtration. Concentration under vacuum followed by separation of the precipitate by decantation and filtration constitutes a first stage of purification of the method accord ing to the invention, during which biflavonoids and other hydrophobic substances are removed.The filtrate is then treated with ammonia solution so as to adjust the pH to approximately 9. A precipitation of the proanthocyanidins is thereby obtained. The insoluble fraction which precipitates is then filtered for the purpose of removing the proanthocyanidins. Alkalinization of the filtrate followed by filtration of the proanthocyanidins constitutes the second essential stage of purification of the method according to the invention. The pH of the filtrate is then adjusted by acidification using sulfuric acid to bring the pH of the filtrate back to a value in the region of 2. The filtrate is then extracted with approximately 1.250 liter of a butanone/acetone (70:30) mixture in the presence of approximately 650 g of ammonium sulfate. The organic phase obtained during this liquid-liquid extraction is then treated with an additional approxi mately 200 g of ammonium sulfate, and thereafter filtered, concentrated and taken to dryness under reduced pressure. This dry extract is then taken up in 8 volumes of aqueous ethanol,

and thereafter washed with a further 2 volumes of aqueous ethanol. The suspension thereby obtained is then filtered so as to remove the insoluble fraction therefrom. The final extract is thereby recovered by concentrating the alcoholic filtrate and taking it to dryness under reduced pressure. The yield by weight is 90%

Uses:

In vitro studies of ginkgo extracts indicate anti-infective, chemopreventive,anticancer, and cytotoxic effects. Epidemiological data indicate that ginkgo may play a role in reducing the risk of ovarian cancer. However, data from the Gingko Evaluation of Memory (GEM) study, in which cancer risk was the secondary outcome, do not support gingko's effectiveness in reducing cancer risk. Studies in patients with gastric cancer showed reduction in tumor area following oral supplementation with capsules of ginkgo exocarp polysaccharides' combination of an injectable form of ginkgo extract and 5-fluorouracil improved the quality of life of patients with advanced colorectal cancer. Further studies are needed to determine the anticancer potential of ginkgo supplements.

3. **Psoralea corylifolia**

Fig 4: Psoralea corylifolia

Scientific Name : Psoralea corylifolia

Common Name: Bakuchi

Family: Fabaceae

Kingdom: Plantae

Genus: Sporalea

Colour: Yellow and bluish purple

Odour: Strong nutty scent

Taste: Bitter

Part Of Use: Seeds

Chemical Constituents:

Babchi seeds contain an essential oils (0.05%), a nonvolatile trepenoid oil, a dark brown resin (8.6%), a pigment (hydroxyflavone), a monotrepnoid phenol named bakuchiol, a brown fixed oil (10%), raffinose and coumarin compounds (psoralen, isopsoralen, psoralidin, isopsoralidin and corylifolin), albumin, sugar, ash 7.5% and a trace of manganese. Psoralen and isopsoralen are considered the therapeutically active constituent of the seeds. Fixed oil is on keeping deposits psoralen. It contains resin acid (21.5%); stigmasterol is present in the unsaponifiable matter. Essential oil and unsaponified oil are pharmacologicaly active. They used in case of leucoderma and psorias.

Extraction process:

The fresh samples (1g, each) of plant tissue were crushed with liquid nitrogen carefully and were soaked in ethanol for 24h under dark and then homogenized using pestle and mortar. They were followed as such in the pestle till the time than that ethanol gets evaporated. After evaporation of ethanol, the semisolid form of extract was mixed in methanol (HPLC grade). This mixture was transferred to centrifuge tube and centrifuged for 15min at 12000rpm at room temperature there. The supernatant was filtered using 0.22mm Millipore filter.

Uses:

The Bakuchi extract is found to be effective in destroying the cancer cells of osteosarcoma and lung cancer. Bakuchi extract can also destroy the cancer cells containing multi-drug resistant the Human papillomavirus.

4. **Common Nettle**

Fig 5: Common Nettle

Scientific Name: Urtica dioica

Common Name: Stinging nettle

Family: Urticaceae

Genus: Urtica

Kingdom: Plantae

Colour : Dark green

Odour: faint and herbaceous with a slightly bitter, slightly salty, pleasant, herbaceous flavor.

Taste: tastes like spinach, but a bit punchier

Part Of Use: Leaf

Chemical Constituents:

Nettle has agglutinin, acetophenone, alkaloids, acetylcholine, chlorogenic acid, butyric acid, chlorophylll, caffeic acid, carbonic acid, choline, histamine, coumaric acid, formic acid, pantothenic acid, kaempferol, coproporphyrin, lectin, lecithin, lignan, linoleic and linolenic acids, palmitic acid, xanthophyll, quercetin, quinic acid, serotonin, stigmasterol, terpenes, violaxanthin, and succinic acid in its chemical content. Nettle also contains 2,5% fatty substance, 14–17% albumins, and 18% protein in dry matter. Seeds of nettle contain 8–10% fixed oil. 1 kg fresh plant contains 130 mg vitamin C, 730 mg carotene, and oxalate. Stinging hair of nettle contains formic acid, histamine, and acetylcholine. Leaves of nettle contain provitamin A, vitamin B_1, K, xanthophylls, and sistosterin and ashes of nettle contain 6,3% ferric oxide, potassium, calcium, and silicium

Extraction Process:

Shake your stinging nettle roots to knock off most of the dirt. Using pruning shears or scissors, clip off the leaves and dead stems that remain attached to the roots. Fill a sink with cool water and swish the roots through the water to remove any additional dirt. Line a wicker basket with a towel.

Uses:

The leaf extract of Urtica dioica has been reported to improve glucose homeostasis in vivo. Nettle root could prevent some of the effects of prostatic hyperplasia. Extracts of nettle leaf are used as anti-inflammatory remedies for rheumatoid arthritis. Urtica dioica extract significantly increased the sensitivity of breast cancer cells to paclitaxel (Dhouibi et al., 2019). Franciškovi ć et al., (2017) reported that Urtica dioica L. is a candidate for the development of phytopharmaceuticals or dietary supplements for cotreatment of various inflammatory diseases, particularly inflammatory bowel diseases.

5. Green Tea

Fig 6: Green Tea

Scientific Name : Camellia sinesis

Common Name : Green Tea

Family : Theaceae

Genus : Camellia

Kingdom : Plantae

Color : Bright green

Odour: fresh, floral and tender fragrance

Taste: bitter and astringent

Part Of Use: Leaves

Chemical Constituents :

Green tea contains polyphenols, which include flavanols, flavandiols, flavonoids, and phenolic acids; these compounds may account for up to 30% of the dry weight. Most of the green tea polyphenols (GTPs) are flavonols, commonly known as catechins.

Extraction Process:

For hot water extraction, the green tea powder (0.50 g) and 85 °C water (18 mL) were mixed in a 50 mL centrifuge tube with a certain liquid/solid ratio, and the extraction was carried out at room temperature (25 °C) for a certain time. After extraction, the crude extract was centrifuged at 12,000× g for 10 min.

Uses:

Some laboratory studies have shown that extracts from green tea can stop cancer cells from growing. Green tea contains substances called polyphenols. A sub group of these polyphenols is called catechins. It inhibits proliferation of many tumor types in culture but has also been show to inhibit neovascularization promoted by Vascular Endothelial Growth Factor (VEGF).

5. **Ginger**

Fig 7: Ginger

Scientific Name : Zingiber officinale

Common Name: Ginger

Colour: Pale yellow

Odour: Zingiber ales

Taste: Slightly biting taste

Family: Zingiberaceae

Kingdom: Plantae

Genus: Zingiber

Species: Z. officinale

Part of Use: Rhizomes

Chemical Constituents:

Ginger is abundant in active constituents, such as phenolic and terpene compounds. The phenolic compounds in ginger are mainly gingerroots, shogaols, and paradols. In fresh ginger, gingerols are the major polyphenols, such as 6-gingerol, 8-gingerol, and 10-gingerol.

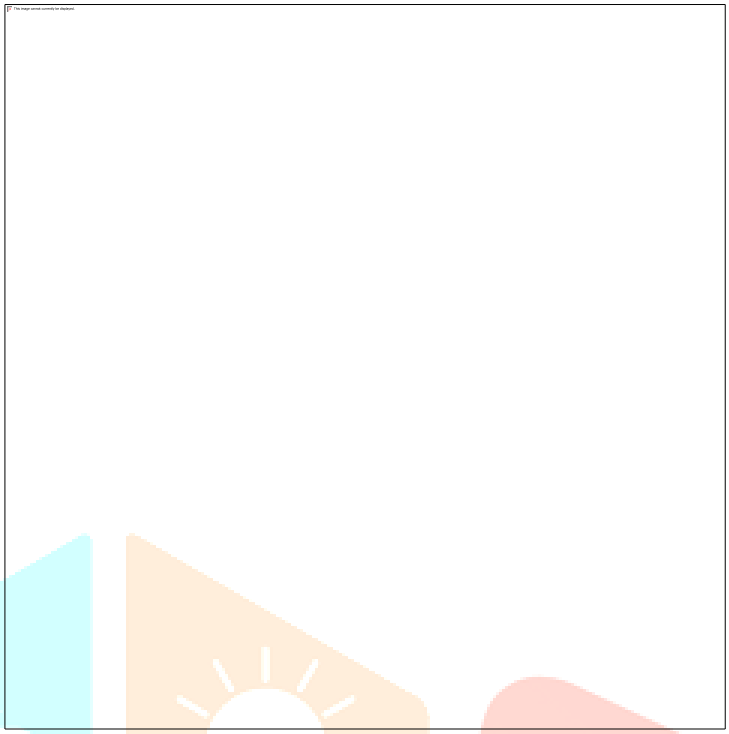
Extraction Process:

Ginger is used as a raw material, and volatile oil of an aroma component of the ginger is extracted by a water steam distillation method. Cold pressing ginger oil of a pungent taste component of the ginger is extracted by a centrifugal separation method. An excipient is used for granulation, and the yellowish solid ginger extract is made. The method of the present invention has the advantages of simple manufacture technology and high utilization rate of the ginger. The spicy component in the ginger is effectively extracted, and the quantity of the spicy component in the product is equivalent to more than 12 times of that of the ginger. The ginger extract is in a solid form and is easily water-soluble. The ginger extract has the advantages of convenience for eating, storage and transportation.

Uses:

the anticancer activity of the ginger extract in pancreatic cancer is poorly understood. Here, we demonstrate that the ethanol-extracted materials of ginger suppressed cell cycle progression and consequently induced the death of human pancreatic cancer cell lines, including Panc-1 cells. The underlying mechanism entailed autosis, a recently characterized form of cell death, but not apoptosis or necroptosis. The extract markedly increased the LC3-II/LC3-I ratio, decreased SQSTM1/p62 protein, and enhanced vacuolization of the cytoplasm in Panc-1 cells. It activated AMPK, a positive regulator of autophagy, and inhibited mTOR, a negative autophagic regulator. The autophagy inhibitors 3-methyladenine and chloroquine partially prevented cell death. Morphologically, however, focal membrane rupture, nuclear shrinkage, focal swelling of the perinuclear space and electron dense mitochondria, which are unique morphological features of autosis, were observed.

COPTIS CHINENSIS,



the Chinese goldthread, is a herb used as a traditional medicine in China thus officially enlisted in the Chinese pharmacopeia. It is widely known for its traditional use against various diseases like diarrhea, dysentery, acute febrile, and supportive infections. The organic extract of C. chinensis possesses anti-inflammatory and anti-oxidant properties . C. chinensis extract has wide use in the treatment of cholera, dysentery, diabetes, blood and lung cancer because of its strong antibacterial activity. Coptis genus contains the most important and active components, such as an alkaloid i.e., berberine . Berberines alkaloids are used frequently as criteria in the quality control of Rhizoma coptidis (Huang Lian) products and lead to the apoptosis of human leukemia HL-60 cells by down regulating nucleophosmin/B23 and telomerase activity.

CONCLUSION

Natural products extracted from plants are a rich source for anticancer agents. Multiple cancer hallmarks are targeted by plant-derived natural products through altering diverse signaling pathways. Some natural products such as curcumin and resveratrol exhibit the ability to target cancer through multiple mechanisms. Apoptosis induction is the most common pathway activated by plant-derived natural products. Targeting drug resistance and metastasis inhibition were also reported as anticancer mechanisms of these compounds. The use of plant-derived natural products as an adjuvant therapy with conventional treatments is a productive strategy that deserves further investigations to improve cancer treatment protocols.

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