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NOVEL BIOACTIVE NATURAL PHYTOCONSTITUENTS WITH PRONOUNCED CHEMOTHERAPEUTIC POTENTIALS

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ABSTRACT

Cancer is the second leading cause of death in the world, with 8.8 million people dying each year. Men are more likely to develop kidney cancer, prostate cancer, colorectal cancer, stomach cancer, and liver cancer, while women are more likely to develop breast cancer, colorectal cancer, lung cancer, cervix cancer, and stomach cancer. Several medications licensed for use in cancer treatment by the US Food and Drug Administration (USFDA) are extracted from plants, like taxanes like paclitaxel and vinca alkaloids like vincristine and vinblastine. Even so, there is an urgent need to find a variety of bioactive sources in order to produce a new anti-cancer treatment to treat this chronic disease. To date, more than thirty natural products extracted from plants have been isolated and are being used in clinical trials. Novel therapeutic agents derived from bioactive sources have been shown to be clinically active against different forms of cancer cells, according to a literature review of various articles and texts. The focus of the current analysis is on novel therapeutic agents derived from plants that have the ability to treat a variety of cancers, as shown by clinical trials. The most important observations of these successful novel therapeutic agents were also presented and explored in this article.

KEYWORDS: Natural, Phytoconstituents, Anti-cancer, Chemotherapeutics, Cancer, Therapy.

INTRODUCTION

Cancer is a group of diseases marked by abnormally accelerated cell division in the human body, which results in death. Cancer begins with a series of specific DNA mutations that aid cellular growth and proliferation.[1] These cells are conceived, infiltrate, and kill regular cells, resulting in a body imbalance. Mutations are repaired of the DNA milieu in regular cells; moreover, cancerous cells neglect their capacity to restore themselves.[2] Tobacco use, alcohol use, obesity, low dietary fiber intake, excessive red meat use, smoking, higher salt, and saturated fat use, ionizing and non-ionizing radiation, reduced ingestion of fruits and green vegetables, and several carcinogenic infectious agents such as chronic *Helicobacter pylori* infections, hepatitis B, and hepatitis C Melatonin (*N*-acetyl-5-methoxytryptamine) has long been recognized as a chemoprotective substance.[3] The pineal gland in vertebrates secretes a tiny lipophilic indoleamine hormone. Apart from vertebrates, it has been included in a variety of eukaryotes algae, the dinoflagellate *Lingulodinium polyedrum* (syn. *Gonyaulax polyedra*), cereals (*Oryza sativa*), fruits (*Vitis vinifera*, *Fragaria ananassa*), vegetables, and others.[4] Melatonin is biosynthesized naturally from the amino acid tryptophan using a number of catalytic enzymes in four stages. Melatonin has a strong apoptotic effect on Ehrlich tumors, colorectal cancer cells, breast cancer cells, and liver cancer cells. Melatonin has recently been discovered to have oncostatic, anti-angiogenic, and anti-metastatic effects, as well as an inhibitory action on NF-kB in a variety of mammary and liver cancer cells.[5]

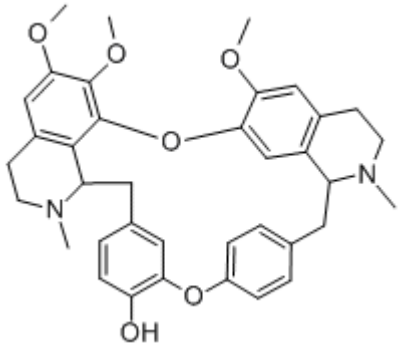
According to a new World Health Organization (WHO) survey, it is the second leading cause of death worldwide, with over 10 million deaths to date. In general, a 2-3 percent annual mortality rate for cancer patients has been observed.[6] According to the Global Burden of Cancer Study (GLOBOCAN)'s annual report, there were 14.1 million incidents and 8.2 million fatalities. According to researchers, there will be at least 15 million additional cases every year before 2020. [7] Still, (under)developed countries bear the brunt of the patient load, accounting for 65% of global cancer deaths. Lung cancer is the leading cause of death in men, while breast cancer is the leading cause of death in women in (under)developed countries. This mismatch has been treated and corrected with new medication interventions. Despite the fact that billions of dollars have been invested in cancer study and care, the cause is still unknown.[8]

Several chemopreventive agents have been used to treat various cancer types, but their non-selective cytotoxic activity has limited their usage. Because of their anti-oxidant, chemoprotectant, and free-radical scavenging properties, dietary fruits and vegetables have been shown to decrease the incidence of various cancers.[9] Currently, traditional medicine, ethnomedicines, and natural products are used by 80% of the world's population. Orthodox ethnoherbal therapy has been responsible for the discovery of almost 75% of all commercially available pharmaceuticals.[10]

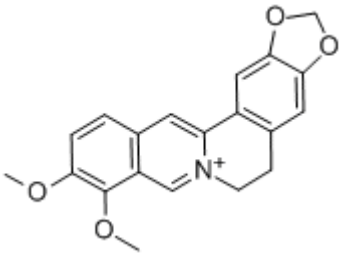
ROLE OF SECONDARY METABOLITES

Natural bioactive secondary metabolites derived from herbal sources have been used to manage a variety of cancers throughout history. Hartwell has classified over 3000 bioactive ingredients from herbal sources into low to moderate anti-cancer action categories.[11] The US Food and Drug Administration (FDA) authorized a collection of novel anticancer agents, with the bulk of the compounds coming from natural sources and just a few pure synthetic molecules, according to Newman and Cragg. Flavonoids, carotenoids, polyphenolic compounds, and terpenoids, among other bioactive secondary metabolites from plants, have been shown to be innovative medical agents for cancer treatment.[12] *Betula alba, Camptotheca acuminate, Catharanthus roseus, Centaurea schischkinii, Cephalotaxus species, Curcuma longa, Erythroxylum pervillei, Ipomoeca batatas, Podophyllum species, Taxus brevifolia*, and other common medicinal plants contain numerous bioactive anti-cancer agents. Vinca alkaloids, taxane diterpenoids, epipodophyllotoxin lignans, and camptothecin quinoline alkaloid derivatives are the main groups of anti-cancer components found in plants.[13]

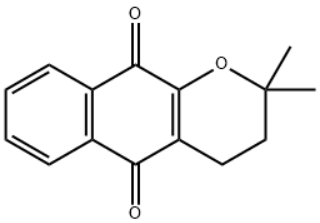
ANTI-CANCER PHYTOCONSTITUENTS



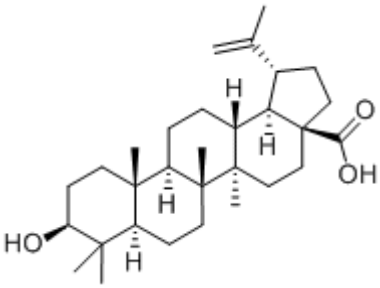
Berbamine



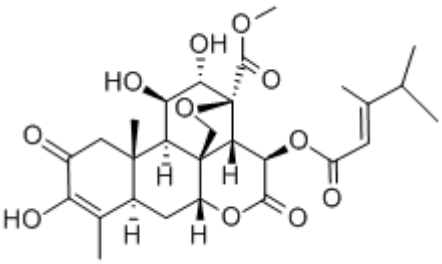
Berberine



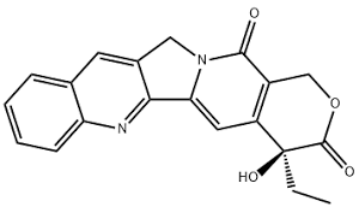
Beta-lapachone



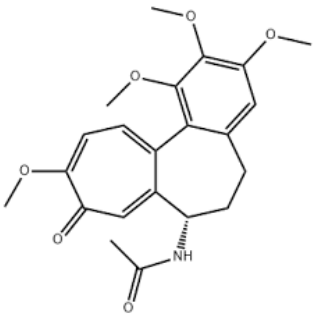
Betulinic acid



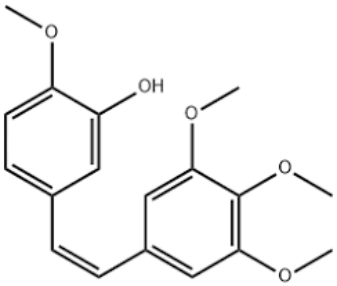
Bruceantin



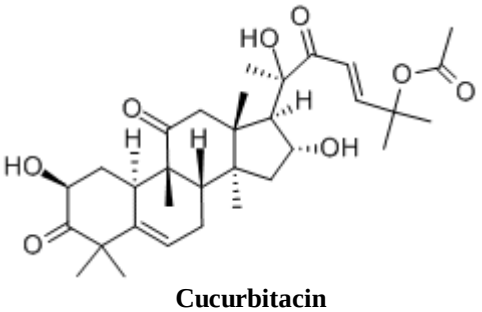
Camptothecin



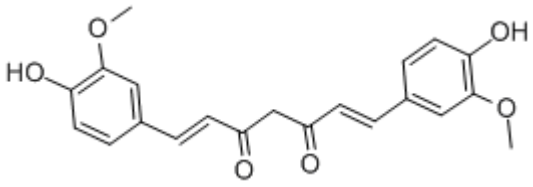
Colchicine



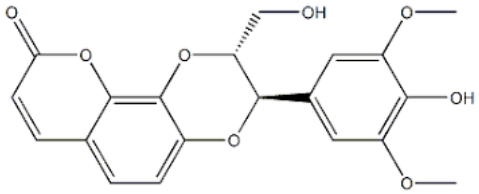
Combretastatin A-4



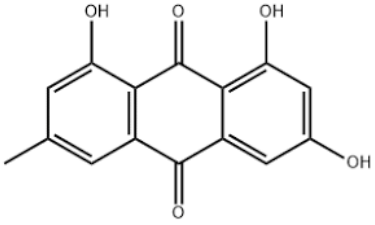
Cucurbitacin



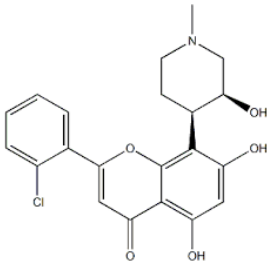
Curcumin



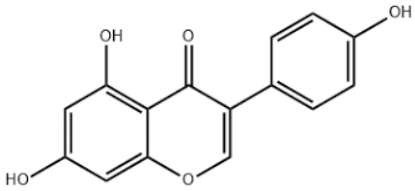
Daphnoretin



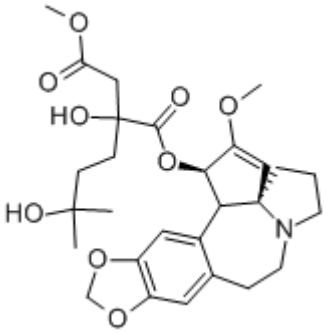
Emodin



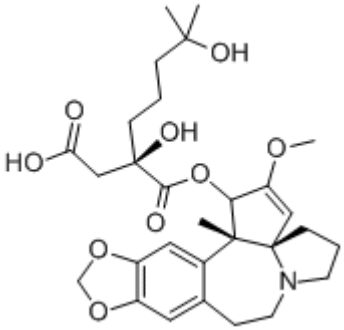
Flavopiridol



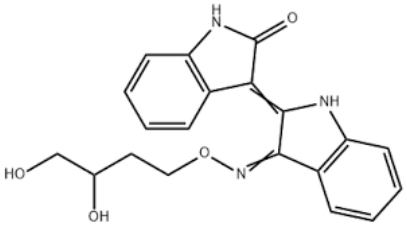
Genistein



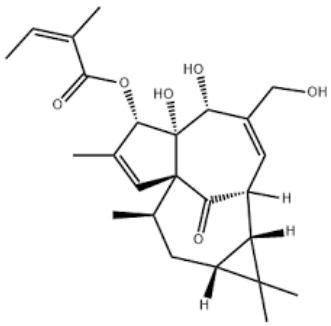
Harringtonine



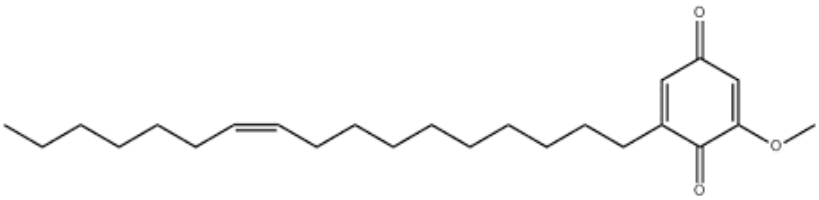
Homoharringtonine



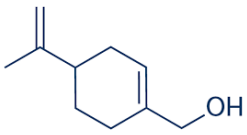
Indirubin



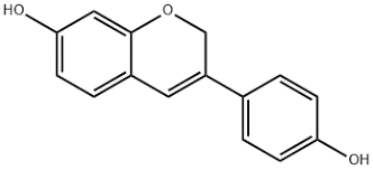
Ingenol 3-O-angelate



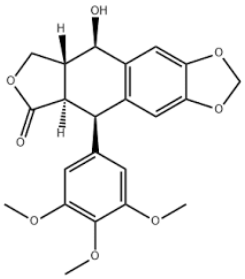
Irisquinone



Perillyl alcohol



Phenoxodiol



Podophyllotoxin

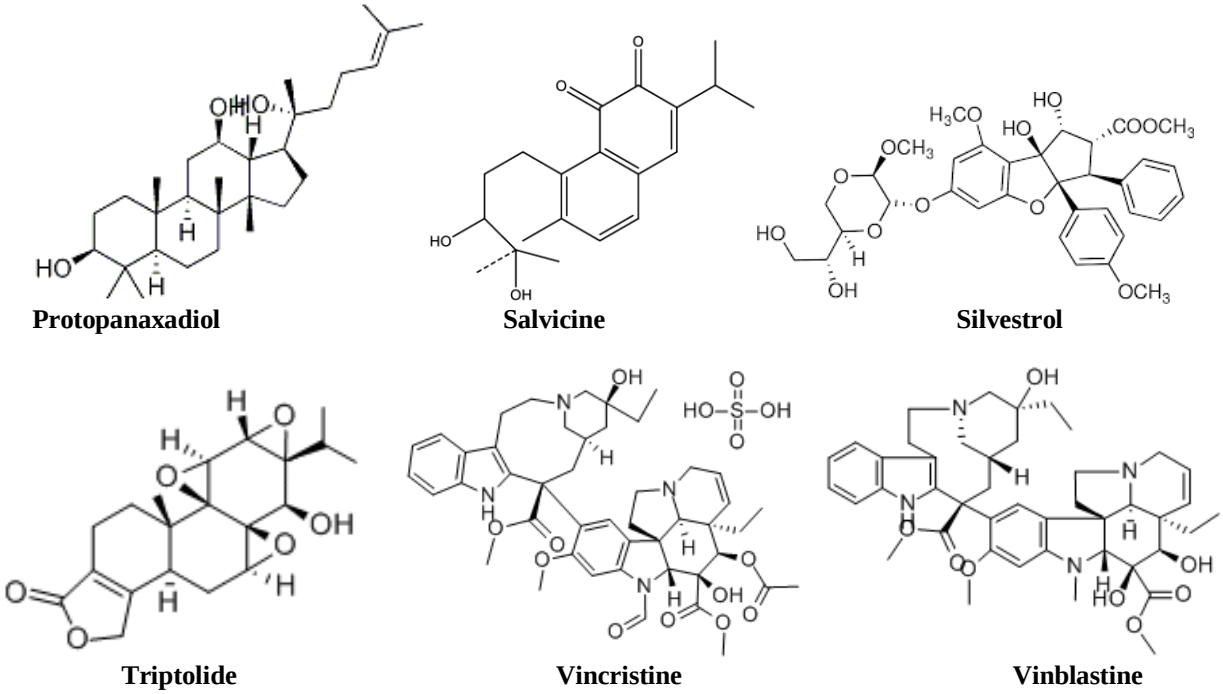


Figure 1. Structure of some prominent anti-cancer phytoconstituents.

Berbamine

Berbamine (**Figure 1**), a bisbenzylisoquinoline alkaloid, was extracted from the Chinese herb *Berberis amurensis* (Berberidaceae). The phytochemical inhibits the BCR/ABL tyrosine kinase and effectively increases cell apoptosis, making it useful in the treatment of chronic myeloid leukemia via a survivin-mediated mechanism, the substance also causes caspase-3-dependent apoptosis in leukemic NB4 cells.[14]

Berberine

Berberine is a quaternary ammonium salt with an isoquinoline moiety that can be found in *Berberineeris species* (Berberidaceae), *Hvdrastis Canadensis* L. (Ranunculaceae), and *Arcungelisia fault* (Menispermaceae). They phytocompounds showed effective anti-tumor action *in vivo* and *in vitro* against active cancers such as breast cancer, kidney cancer, liver cancer, prostate cancer, and osteosarcoma.[15]

Beta-lapachone

β-lapachone (3,4-dihydro-2,2-dimethyl-2*H*-naphthol [1, 2-β] pyran-5, 6-dione), a water-insoluble orthonapthoquinone compound isolated from the heartwood of *Tabebuia avellanedae*, is a topoisomerase-I and topoisomerase-II substrate. It is a promising anti-cancer drug used to combat kidney cancer, pancreatic cancer, blood cancer, lung cancer, and breast cancer. The erratic delivery, low aqueous solubility, and systemic toxicity of the phytoconstituents have currently been overcome by utilizing gold nano-carriers to increase clinical competence in cancer therapy.[16]

Betulinic acid

Betulinic acid (3-hydroxy-lup-20(29)-en-28-oic acid), a pentacyclic triterpenoidal compound derived from *Betula alba*'s white bark, is a pentacyclic triterpenoidal compound. By stimulating the mitochondrial process of apoptosis, which facilitates cancer cell death, the phytochemical has important anti-cancer efficacy.[17]

Bruceantin

Bruceantin, a quassinoid derived from *Brucea species* (Simaroubaceae), has anti-tumor properties in cancer cells. In rabbit reticulocytes, HeLa cells, and reticulocyte lysates, Bruceantin inhibits protein synthesis. There are also reports of some secondary effects on DNA biosynthesis.[18]

Camptothecin

Camptothecin (CPT), a cytotoxic alkaloid, was extracted from the stem and bark of *Camptotheca acuminate*, a Chinese ornamental tree. A pentacyclic ring arrangement with pyrrole (3,4) and quinoline moiety makes up CPT. The anti-cancer activity of the CPT molecule is due to an S-configured lactone ring and a carboxylate group. Because of its low water solubility and extreme toxicity, analogs of CPT such as topotecan, irinotecan (CPT-11), 9-aminocamptothecin (9-AC), lurtotecan, and rubitecan were synthesized to address these drawbacks. Anagoges work by inhibiting DNA topoisomerase-I, a protein that is important for DNA replication and transcription. Topotecan has been shown to be successful as second-line therapy in patients with epithelial ovarian cancer and small cell lung cancer. Irinotecan may be used as a first-line therapy or second-line therapy for metastatic colorectal cancer. Similarly, DX-8951f (Exatecan), a recent semi-synthetic analog, showed strong anti-cancer

efficacy *in vitro* and *in vivo* against a variety of tumors. In comparison to CPT and other derivatives, these semi-synthetic analogs seem to have improved aqueous solubility, strong tumor efficiency, and less toxic effects. When opposed to CPT-11, the active metabolite SN-38 (7-ethyl-10-hydroxycamptothecin) has a potent anti-tumor effect. In laboratory species, CZ-48 functions as a novel anti-cancer agent of low toxicity.[19]

Colchicine

Colchicine is a toxic natural product and the secondary metabolite derived from the plant *Colchicum autumnale*, also known as meadow saffron that is used to treat solid tumors and leukemia cells. Colchicine causes effective mitotic arrest during metaphase, prompting the development of other powerful molecules such as thiocolchicocide, colchicoside, 3-demethyl colchicine, and others. The toxic impact has remained a draw for researchers working on semi-synthetic substances for anti-cancer treatment around the world.[20]

Combretastatin A-4

Combretastatin A-4 is a stilbene compound derived from the South African bush willow tree *Combretum caffrum* Kuntze, which belongs to the Combretaceae genus. The extremely water-soluble prodrug combretastatin A-4 disodium phosphate is reportedly in Phase-II clinical trials. The compound prevents angiogenesis, alters the composition of endothelial cells, and disrupts the tubulin structure, preventing cancer cells from receiving nutrients.[21]

Cucurbitacin

Cucurbitacin is a biological substance derived primarily from the cucurbitacin family. It's a tetracyclic triterpenoid with anti-cancer properties against cancer cells. According to the literature, the I and B types may be used to treat different cancers of the breast, stomach, prostate, nasopharynx, and head by inhibiting JAK2 and STAT3, which stimulate cancer cell apoptosis and inhibit cell development. Polymeric micelles are used for innovative drug delivery because of their water insolubility and higher toxicity.[22]

Curcumin

Curcumin (4-hydroxy-3-methoxyphenyl) is a polyphenolic medicinal agent isolated from the rhizomes of *Curcuma longa* (Zingiberaceae), also known as turmeric or Indian saffron, which has been shown to have anti-cancer properties. Turmeric's yellow color is attributable to the existence of a pigment called curcuminoids. Curcumin's precise function is yet to be determined. It is thought to influence the cell cycle process and promote apoptosis in various cancer cells. Curcumin completed its Phase-I clinical trial with flying colors, and no side effects have been identified at large doses. Curcumin is currently being used in Phase-I/Phase-II studies for colorectal cancer, multiple myeloma, and pancreatic cancer. Curcumin has a broad variety of medicinal applications, including anti-oxidant and anti-inflammatory effects, in addition to anti-cancer properties. Curcumin has the capacity to prevent carcinogen bioactivation by suppressing various cytochrome P_{450} isozymes, as well as trigger step-II carcinogen detoxifying enzyme action or speech. In prostate cancer cells, a combination of phenethylisothiocyanate and curcumin therapy triggered suppression of epidermal growth factor receptor (EGFR) phosphorylation, inhibition of epidermal growth factor (EGF)-induced phosphorylation, and activation of phosphatidylinositol 3-kinase (PI3K). Multiple cell signaling pathways, including cell proliferation, cell survival, caspase activation, tumor suppressor pathway, death receptor pathway, mitochondrial pathways, and protein kinase pathway, suppress tumor cell development.[23]

Daphnoretin

Also known as 7-hydroxy-6-3-2*H*-hydroxy-2*H*-carvimen-2*H*-chromene-thidaphne-7-ol, a daphnoretinoylactone is a glycoside derived from the root bark of the plant, the *Wikstroemia indica* in the Thymelaceae family. Ehrlich ascites extracts are capable of suppressing DNA synthesis and decreasing protein synthesis in human hepatocellular carcinoma cell lines. It has been written in the literature that in Hep-3, the consumption of food phytates can block the expression of hepatitis-B antigen expression.[24]

Ellipticine

It was discovered that *Ochrosia elliptica* (5,11-dimethyl-6*H*-pyrido-[4,3-b] carbazole)maltic acid and its derivatives could be used in their total form. Various cancer cells might have an elliptical capacity for increased malignancy with respect to resistance to curability. a topoisomerase-II inhibitor that interferes serves between the top DNA strands, thereby loosening and breaking the topology and in addition, it has also been documented to hamper cell proliferation as well as triggering cell death in Hep-2 cells to self-destruct (human hepatocellular carcinoma).[25]

Emodin

From the rhizome emodin (a portion contained in the Polygonaceae family), an apoptotic effect was shown in several cancer types where the route of application involved increased its rate of excretion and treatment in lung cancer, ovarian cancer, and blood cancer by around 20-fold.[26]

Flavopiridol

This plant in the Pacific region had the pleasure of popularity brought to it by the effects of its alkaloids, dystoninidamodin (flavopolynylimine), which became infamous for its G_1/M and G_2/S phases in non-lymphoma, non-Hodgkin's lymphoma, and lung cancer due to cyclin-dependent kinase (CDK) activity and acts by blocking G_2/M and G_1/S stages. The research on the molecule is present in the second Phases (IIa and IIb) for different types of malignancies.[27]

Genistein

The growth rate of plants has been observed to be equivalent to or slightly greater than 4',5,7-trihydroxyisovalerate (Genistein) and similar to that of these other legumes, *Pueraria lobate, Lupinus species, Psoralea corylifolia, and Vicia faba,* Oxidative metabolism inhibition has been identified as being crucial to tumor growth of the breast cancer, the liver cancer, the prostate cancer, the lung cancer, the ovaries cancer, and the urinary tract cancer.[28]

Harringtonine and Homoharringtonine

Harringtonine and homoharringtonine, two well-known anti-cancer alkaloid esters of cephalotaxine, were extracted from the evergreen coniferous shrubs of the popular Chinese medicine *Cephalotaxus. Cephalotaxus hainanensis, Cephalotaxus qinensis, and Cephalotaxus harrintonia* ideals have been tested for their ability to inhibit a number of cancer cells. Both compounds are used to treat acute and chronic myeloid leukemia (A/C-ML) by inhibiting protein synthesis and modulating the translation mechanism in a homogeneous mixture.[29]

Indirubin

Isadventricularis, which had shown anti-tumor chemoactivity through the cell cycle control of enzymes including suppressing the biosynthesis of cyclin and causing apoptosis as well as arresting cell proliferation by multiple mechanisms, appeared to have in clinical studies to expand the therapeutic capabilities of Chinese herbs to the following effects, such as protecting the DNA and blocking cell cycle, promoting apoptosis, and inhibiting cell growth It is also known to be therapeutic for CML, but issues in solubility and bioavailability presented an obstacle. In the instance of raising the rings, mebamide has been prepared as a second-generation derivative, methylisosindigo (indirubin) has been coined.[30]

Ingenol 3-O-angelate

Ingenol 3-O-angelate (PEP-005) is a diterpene ester ingenol derivative extracted from the plant *Euphorbia peplus* L. PEP-005 is a diterpene ester ingenol derivative isolated from the plant Euphorbia peplus L. The molecule stimulates PKC, resulting in cancer cell necrosis and, ultimately, tumor cell death. PEP-005 is currently undergoing Phase-II clinical trials for the prevention of basal cell carcinoma and actinic keratosis.[31]

Irisquinone

Iridaceaelatea pallasii and *Iris kumaoensis* (Iridaceae) contain irisquinone, a benzoquinone that has shown promise as a chemosensitizer and anti-activity against transplantable rodent tumors.[32]

Montamine

Centaurea montana (Asteraceae) seeds contain the dimeric indole alkaloid montamine, which has anti-colon cancer effect.[33]

Perillyl alcohol

Limonene, a monocyclic monoterpene, is abundant in savin, cranberries, ginger grass, mints, cherries, lavenders, caraway, lemongrass, perilla, wild bergamot, celery seeds, and sage, as well as its naturally occurring product perillyl alcohol. Because of its ability to stop cell division in the G_1 process, the monoterpene portion has been used effectively in cancers of the prostate, breast, non-small cell lung, and colon.[34]

Pervilleines

The pervilleines-A, pervilleines-B, pervilleines-C, and pervilleines-F tropane alkaloid aromatic esters isolated from the roots of *Erythroxylum pervillei* have been shown to be outstanding inhibitors of P-glycoprotein (P-gp) induced drug efflux, which greatly increases cancer chemotherapy by resolving multidrug resistance.[35]

Phenoxodiol

Phenoxodiol is a semisynthetic analog of the naturally occurring plant secondary metabolites isoflavone and genistein (2*H*-1-benzopyran-7-1,3-[4-hydroxyphenyl]). Phenoxodiol inhibits plasma membrane electron transfer and cell proliferation, leading to apoptosis in a variety of cancer cell lines. Phenoxodiol is a chemosensitizer that is presently being used in Phase-III clinical trials for the prevention of breast cancer, as well as in the early phases of clinical trials for prostate and cervical cancer.[36]

Podophyllotoxin

Podophyllotoxin is a resinous secondary metabolite contained in Podophyllum species' rhizomes and roots. In the 1880s, the constituent was first extracted from the plant *Podophyllum hexandrum, Podophyllum peltatum* Linn, and *Podophyllum emodi* Wallich, and the form was discovered 70 years later. It's available as epipodophyllotoxin, a stereoisomeric type that also serves as a substrate for the synthesis of two biologically active principles: etoposide and teniposide, which are used to treat cancers of the lymph nodes, testes, and lungs.[37]

Protopanaxadiol

Protopanaxadiol (Pandimex^{TM}) is a tetracyclictriterpene saponin glycoside derived from *Panax ginseng* (Korean species) and *Panax notoginseng* (Chinese species) that inhibits the cell cycle by various signaling mechanisms, resulting in cancer cell death. Protopanaxadiol, an effective P-gp antagonist, has the ability to destroy multidrug-resistant tumors. It is also used to combat tumors of the breast, colon, rectum, lung, and pancreas. Protopanaxadiol is now undergoing a Phase-I clinical trial for the prevention of lung cancer and solid tumors, according to the literature.[38]

Salvicine

Salvicine is a novel diterpenoid quinone obtained as a derivative of saprorthoquinone, a naturally occurring lead contained in *Salvia prionitis* Hance (Labiatae).

Salvicine has potent topoisomerase-II inhibitory activity *in vitro* and *in vivo* against malignant tumors.[39]

Schischkinnin

Schischkinnin is a novel anti-cancer indole alkaloid obtained from the seeds of *Centaurea schischkinii*, a member of the Asteraceae family. Three flavonoids; astragalin, afzelin, and apigenin, as well as lignin components matairesinol, matairesinoside, arctigenin, and arctiin, all derived from the same herb, have shown potent colon cancer involvement.[40]

Silvestrol

Silvestrol is a bioactive anti-cancer compound isolated from *Aglaia foveolata* Pannell's twigs and fruits (Meliaceae). Episilvestrol, a semisynthetic epimer, was recently created, but its cytotoxicity is lower. The ability to fight breast cancer, prostate cancer, and lung cancer helped one of the promising molecules achieve notoriety. The plant metabolite works by causing caspase-2, caspase-9, and caspase-10 to cause apoptosis (programmed cell death) in LNCaP (hormone-dependent human prostate cancer) cells.[41]

Taxanes

Paclitaxel (Taxol®) is a complex diterpene taxane that was discovered in the bark of *Taxus brevifoli* (Himalayan yew tree) and *Taxus baccata* (European yew tree) belonging to the Taxaceae family. Their structure was first elucidated and described in 1971, and they have been used to treat different forms of cancer cells since the 1990s. Paclitaxel is a water-insoluble, poisonous compound from which Docetaxel, a water-soluble compound, was semi-synthesized. Docetaxel (Taxotere®), a semi-synthetic version of paclitaxel, was shown to be more successful in the treatment of cervical, breast, and lung tumors, as well as colon, kidney, melanoma, esophageal, and other solid tumor cancers and Kaposi's sarcoma. Both docetaxel and paclitaxel are used in the management of metastatic cancer, breast cancer, lung cancer, cervical cancer, prostate cancer, and lymphoid malignancies, among other cancers. Increased tubulin polymerization is the mode of operation. As a result, the microtubules are reinforced, and depolymerization is prevented.[42]

Triptolide

Triptolide is a diterpenoid epoxide derived from the popular Chinese medication *Tripterygium wilfordii* Hook F. This chemical moiety promotes tumor cell apoptosis, which has anti-cancer properties. This chemotherapeutic agent had problems with water solubility and a strong toxic impact, which are now being addressed by creating new derivatives like F60008. PG490-88 (14-succinyl triptolide sodium salt), an anti-prostate cancer derivative, is reportedly in Phase-I clinical trials.[43]

Vinca alkaloids

Vincristine and vinblastine, indole salts, are active anti-cancer compounds found in the Apocynaceae plant Vinca rosea or *Catharanthus roseus*. These alkaloids work by inhibiting cell proliferation by disrupting microtubular dynamics during mitosis cell division, resulting in a characteristic block during mitosis and increased apoptosis. Vinorelbine and vindesine, semi-synthetic analogs with a strong therapeutic index, were synthesized and shown to have substantial efficacy against lymphocytic leukemia. They can also have anti-leukemic, anti-lymphoma, anti-advanced testicular cancer, anti-breast cancer, anti-lung cancer, and anti-sarcoma Kaposi's activity in mice. As opposed to other vinca alkaloids, vinflunine, a bifluorinated analog of vinorelbine, has superior anti-cancer efficacy. Novel vinca alkaloid therapeutic agents are presently being tested in Phase-II clinical trials. In laboratory animal models, both vinflunine and vinorelbine have lower toxicity.[44]

CONCLUSION

Natural products have an important part in the manufacture of anti-cancer treatments. They serve as a framework for the development of semi-synthetic analogs with substantial tumor-suppressing potential. Phytoconstituents often have chemopreventive properties since they modulate different molecular pathways, ingredients, and targets. As a result, they are regarded as a low-cost, quickly approachable, trustworthy, and globally agreed choice. Dietary fruits and vegetables have recently been discovered to be both chemoprotective and effective against neoplasms. Currently, 80 percent of cancer treatments in clinical trials are derived from nature, including lymphomas, bronchial cancer, testicular cancer, chronic myeloid leukemia, osteocarcoma, small cell lung cancer, stomach cancer, colorectal cancer, kidney cancer, ovarian cancer, and breast cancer. This scientific review would offer an overview of phytoconstituents that could be useful in the future for treating cancers in a more patient-friendly manner, as well as opening up potential opportunities for more research and drug production.

CONFLICTS OF INTEREST

No conflict of interest is declared.

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