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Perspectives of Anti-Cancer Phytoconstituents in Pharmacotherapy

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ABSTRACT

With 8.8 million people dying each year, cancer is the world's second largest cause of mortality. Kidney cancer, prostate cancer, colorectal cancer, stomach cancer, and liver cancer are more common in males, whereas breast cancer, colorectal cancer, lung cancer, cervical cancer, and stomach cancer are more common in women. Several medicines, such as taxanes like paclitaxel and vinca alkaloids like vincristine and vinblastine, are derived from plants and are approved by the US Food and Drug Administration (USFDA) for use in cancer therapy. Nonetheless, a range of bioactive sources must be identified as soon as possible in order to develop a novel anti-cancer therapy for this chronic illness. More than thirty plant-derived natural compounds have been identified and are now being tested in clinical studies. According to a literature study of numerous papers and texts, novel therapeutic compounds generated from bioactive sources have been proven to be therapeutically efficacious against various types of cancer cells. The present study focuses on new therapeutic compounds derived from plants that have been proven in clinical trials to cure a range of malignancies. This paper also provided and analyzed the most significant findings of these effective new therapeutic medicines.

Key Words: Natural, Phytoconstituents, Anti-cancer, Chemotherapeutics, Cancer, Therapy

INTRODUCTION

Cancer is a category of illnesses in which the human body's cell division is excessively accelerated, resulting in death. Cancer is caused by a sequence of particular DNA abnormalities that let cells grow and multiply. [1] These cells are created, invade, and destroy normal cells, causing an imbalance in the body. In normal cells, mutations in the DNA milieu are corrected; malignant cells, on the other hand, ignore their ability to repair themselves. [2] Tobacco, alcohol, obesity, low dietary fibre, excessive red meat consumption, smoking, higher salt, and saturated fat consumption, ionising and non-ionizing radiation, reduced intake 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) is a chemoprotective chemical that has been known for a long time. [3] In vertebrates, the pineal gland secretes a small lipophilic indoleamine hormone. It's found in a number of eukaryotes, including algae, the dinoflagellate Lingulodinium polyedrum (syn. Gonyaulax polyedra), cereals (Oryza sativa), fruits (Vitis vinifera, Fragaria ananassa), vegetables, and more. [4] Melatonin is produced naturally in four steps from the amino acid tryptophan by a variety of catalytic enzymes. 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. Melatonin has a strong apoptotic effect on Ehrlich tumours, colorectal cancer cells, breast cancer cells, and liver cancer cells. [5]

It is the second biggest cause of mortality globally, according to a recent World Health Organization (WHO) study, with over 10 million fatalities to date. Cancer patients are estimated to die at a rate of 2% to 3% each year on average. [6] According to the yearly report of the Global Burden of Cancer Study (GLOBOCAN), there were 14.1 million occurrences and 8.2 million deaths. According to experts, by 2020, there will be at least 15 million more instances each year. [7] Despite this, (under)developed nations carry

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the brunt of the patient burden, accounting for 65 percent of cancer deaths worldwide. In (under)developed nations, lung cancer is the main cause of death in males, whereas breast cancer is the leading cause of death in women. With modern pharmaceutical treatments, this mismatch has been addressed and rectified. Despite billions of dollars spent in cancer research and treatment, the cause remains unclear. [8] A variety of chemopreventive medicines have been tried to treat a variety of cancers, but their non-selective cytotoxic action has restricted their utility. Dietary fruits and vegetables have been proven to reduce the incidence of different malignancies due to their anti-oxidant, chemoprotectant, and free-radical scavenging capabilities. [9] Currently, 80 percent of the world's population uses traditional medicine, ethnomedicines, and natural goods. Nearly 75% of all commercially accessible medicines have been discovered thanks to orthodox ethnoherbal treatment. [10]

ROLE OF SECONDARY METABOLITES

Throughout history, natural bioactive secondary metabolites obtained from herbal sources have been utilised to treat a variety of malignancies. Over 3000 bioactive compounds from herbal sources have been categorised by Hartwell into low to moderate anti-cancer activity groups. [11] According to Newman and Cragg, the US Food and Drug Administration (FDA) approved a number of new anticancer medicines, with the majority of the chemicals originating from natural sources and just a handful pure synthesised molecules. Flavonoids, carotenoids, polyphenolic chemicals, and terpenoids, as well as other bioactive secondary metabolites from plants, have been proven to be promising cancer therapy agents. [12] Numerous bioactive anti-cancer compounds may be found in Betula alba, Camptotheca acuminate, Catharanthus roseus, Centaurea schischkinii, Cephalotaxus species, Curcuma longa, Erythroxylum pervillei, Ipomoeca batatas, Podophyllum species, Taxus brevifolia, and other popular medicinal plants. Anti-cancer components found in plants include vinca alkaloids, taxane diterpenoids, epipodophyllotoxin lignans, and camptothecin quinoline alkaloid derivatives. [13]

ANTICANCER PHYTOCONSTITUENTS

Berbamine

Berbamine is a bisbenzylisoquinoline alkaloid derived from Berberis amurensis, a Chinese plant (Berberidaceae). The phytochemical inhibits the BCR/ABL tyrosine kinase and efficiently promotes cell death, making it helpful in the treatment of chronic myeloid leukaemia. It also induces caspase-3-dependent apoptosis in leukemic NB4 cells via a survivin-mediated mechanism. [14]

Berberine

Berberine is an isoquinoline-containing quaternary ammonium salt found in Berberineeris species (Berberidaceae), Hvdrastis Canadensis L. (Ranunculaceae), and Arcungelisia fault (Menispermaceae). Active malignancies such as breast cancer, kidney cancer, liver cancer, prostate cancer, and osteosarcoma demonstrated excellent anti-tumor activity in vivo and in vitro. [15]

Beta-lapachone

A water-insoluble orthonapthoquinone molecule isolated from the heartwood of Tabebuia avellanedae, -lapachone (3,4-dihydro-2,2-dimethyl-2H-naphthol [1, 2-] pyran-5, 6-dione) is a topoisomerase-I and topoisomerase-II substrate. It's a promising anti-cancer medication that's been used to treat kidney cancer, pancreatic cancer, blood cancer, lung cancer, and breast cancer, among other diseases. To improve clinical competence in cancer treatment, gold nano-carriers have been used to overcome irregular delivery, poor water solubility, and systemic toxicity of phytoconstituents. [16]

Betulinic acid

Betulinic acid (3-hydroxy-lup-20(29)-en-28-oic acid) is a pentacyclic triterpenoidal chemical found in Betula alba's white bark. The phytochemical has significant anti-cancer effectiveness by activating the mitochondrial apoptosis mechanism, which promotes cancer cell death. [17]

Bruceantin

In cancer cells, Bruceantin, a quassinoid isolated from Brucea species (Simaroubaceae), exhibits anti-tumor effects. Bruceantin suppresses protein synthesis in rabbit reticulocytes, HeLa cells, and reticulocyte lysates. Some downstream impacts on DNA biosynthesis have also been reported. [18]

Camptothecin

The cytotoxic alkaloid camptothecin (CPT) was isolated from the stem and bark of the Chinese ornamental tree Camptotheca acuminate. CPT is made up of a pentacyclic ring arrangement with pyrrole (3,4) and quinoline moiety. The anti-cancer action of the CPT molecule is attributed to a carboxylate group and an S-configured lactone ring. CPT analogues such as topotecan, irinotecan (CPT-11), 9-aminocamptothecin (9-AC), lurtotecan, and rubitecan were developed to address its poor water solubility and severe toxicity. DNA topoisomerase-I, an enzyme required for DNA replication and transcription, is inhibited by anagoges. In patients with epithelial ovarian cancer and small cell lung cancer, topotecan has been proven to be effective as a second-line treatment. For metastatic colorectal cancer, irinotecan can be used as a first-line or second-line treatment. Similarly, DX-8951f (Exatecan), a recently developed semi-synthetic

derivative, demonstrated potent anti-cancer activity in vitro and in vivo against a range of malignancies. These semi-synthetic analogues seem to have better water solubility, high tumour efficiency, and less adverse effects when compared to CPT and other derivatives. The active metabolite SN-38 (7-ethyl-10-hydroxycamptothecin) exhibits a strong anti-tumor activity when compared to CPT-11. CZ-48 is a new anti-cancer agent with minimal toxicity in experimental animals. [19]

Colchicine

Colchicine is a poisonous natural substance produced from the plant Colchicum autumnale, commonly known as meadow saffron, and is used to treat solid tumours and leukaemia cells. Colchicine induces efficient mitotic arrest during metaphase, leading to the creation of additional potent compounds as thiocolchicocide, colchicoside, 3-demethyl colchicine, and others. For researchers working on semi-synthetic chemicals for anti-cancer therapy all around the globe, the toxic effect has remained an attraction. [20]

Combretastatin A-4

Combretastatin A-4 is a stilbene chemical produced from the Combretum caffrum Kuntze, a South African bush willow tree belonging to the Combretaceae species. Combretastatin A-4 disodium phosphate, a highly water-soluble prodrug, is allegedly in Phase-II clinical trials. Angiogenesis is inhibited, endothelial cell composition is altered, and tubulin structure is disrupted, preventing cancer cells from obtaining nutrients. [21]

Cucurbitacin

Cucurbitacin is a biological compound that is mainly produced from the cucurbitacin family of plants. It's a tetracyclic triterpenoid having cancer-fighting effects. According to the research, blocking JAK2 and STAT3, which promote cancer cell death and limit cell development, may be utilised to treat various malignancies of the breast, stomach, prostate, nasopharynx, and head. Because of their water insolubility and increased toxicity, polymeric micelles are utilised for novel medication administration. [22]

Curcumin

Curcumin (4-hydroxy-3-methoxyphenyl) is a polyphenolic medicinal substance derived from the rhizomes of Curcuma longa (Zingiberaceae), commonly known as turmeric or Indian saffron, with anti-cancer effects. The yellow hue of turmeric is due to the presence of a pigment known as curcuminoids. Curcumin's exact function is yet unknown. In different cancer cells, it is believed to affect the cell cycle and induce apoptosis. Curcumin passed its Phase-I clinical study with flying colours, and there have been no reported adverse effects at high dosages. Curcumin is presently being studied for colorectal cancer, multiple myeloma, and pancreatic cancer in Phase I/II trials. Curcumin has a wide range of therapeutic uses, including anti-oxidant and anti-inflammatory qualities, as well as anti-cancer characteristics. Curcumin has the ability to inhibit different cytochrome P450 isozymes, as well as activate step-II carcinogen detoxification enzyme activity or speech, preventing carcinogen bioactivation. A combination of phenethylisothiocyanate and curcumin treatment suppressed epidermal growth factor receptor (EGFR) phosphorylation, inhibited epidermal growth factor (EGF)-induced phosphorylation, and activated phosphatidylinositol 3-kinase in prostate cancer cells (PI3K). Tumor cell growth is inhibited by many cell signalling pathways, including cell proliferation, cell survival, caspase activation, tumour suppressor pathway, death receptor route, mitochondrial pathways, and protein kinase pathway. [23]

Daphnoretin

A daphnoretinoylactone, also known as 7-hydroxy-6-3-2H-hydroxy-2H-carvimen-2H-chromene-thidaphne-7-ol, is a glycoside produced from the root bark of the Thymelaceae plant Wikstroemia indica. In human hepatocellular carcinoma cell lines, Ehrlich ascites extracts inhibit DNA synthesis while decreasing protein synthesis. The intake of dietary phytates may inhibit the expression of hepatitis-B antigen expression in Hep-3, according to the literature. [24]

Ellipticine

Ochrosia elliptica (5,11-dimethyl-6H-pyrido-[4,3-b] carbazole)maltic acid and its derivatives were found to be usable in their entirety. Various cancer cells may have an elliptical potential for enhanced malignancy in terms of curability resistance. A topoisomerase-II inhibitor that disrupts the topology by interfering with the serves between the top DNA strands, causing the topology to relax and break. It has also been shown to decrease cell growth as well as cause Hep-2 cells to self-destruct (human hepatocellular carcinoma). [25]

Emodin

An apoptotic impact was shown in many cancer types using the rhizome emodin (a part of the Polygonaceae family), where the method of administration enhanced the rate of excretion and therapy in lung cancer, ovarian cancer, and blood cancer by approximately 20-fold. [26]

Flavopiridol

The effects of its alkaloids, dystoninidamodin (flavopolynylimine), became notorious for its G1/M and G2/S phases in non-lymphoma, non-lymphoma, Hodgkin's and lung cancer owing to cyclin-dependent kinase (CDK) activity and acts by inhibiting G2/M and G1/S stages in non-lymphoma, non-lymphoma Hodgkin's The chemical is being

researched in the second phase (IIa and IIb) for several kinds of cancers. [27]

Genistein

Plant growth rates were found to be comparable to or slightly higher than 4',5,7-trihydroxyisovalerate (Genistein), and to be similar to those of Pueraria lobate, Lupinus sp., Psoralea cp., and Vicia faba. Breast cancer, liver cancer, prostate cancer, lung cancer, ovarian cancer, and urinary tract cancer have all been linked to oxidative metabolism suppression. [28]

Harringtonine and Homoharringtonine

Two well-known anti-cancer alkaloid esters of cephalotaxine, harringtonine and homoharringtonine, were isolated from the evergreen coniferous bushes of the traditional Chinese medicinal Cephalotaxus. The potential of C. hainanensis, C. qinensis, and C. harrintonia ideals to inhibit a variety of cancer cells has been investigated. Both drugs limit protein synthesis and modulate the translation process in a homogenous combination to treat acute and chronic myeloid leukaemia (A/C-ML). [29]

Indirubin

Isadventricularis, which had shown anti-tumor chemoactivity through cell cycle control of enzymes, including suppressing cyclin biosynthesis and causing apoptosis as well as arresting cell proliferation by multiple mechanisms, appeared to have expanded the therapeutic capabilities of Chinese herbs in clinical studies to include the following effects, such as DNA protection and blotting. It's also known to be effective against CML, although solubility and bioavailability problems posed a challenge. Mebamide has been produced as a second-generation derivative in the case of increasing the rings, and the term methylisosindigo (indirubin) has been coined. [30]

3-O-angelate Ingenol

PEP-005 is a diterpene ester ingenol derivative isolated from the Euphorbia peplus L. plant. PEP-005 is a diterpene ester ingenol derivative found in the Euphorbia peplus L plant. PKC is stimulated by the chemical, resulting in cancer cell necrosis and, eventually, tumour cell death. PEP-005 is presently being tested for the prevention of basal cell carcinoma and actinic keratosis in Phase II clinical studies. [31]

Irisquinone

Irisquinone is a benzoquinone found in Iridaceaelatea pallasii and Iris kumaoensis (Iridaceae) that has showed potential as a chemosensitizer and anti-activity against transplantable mouse cancers. [32]

Montamine

The dimeric indole alkaloid montamine, found in Centaurea montana (Asteraceae) seeds, possesses anti-colon cancer properties. [33]

Alcohol perillyl

Savin, cranberries, ginger grass, mints, cherries, lavenders, caraway, lemongrass, perilla, wild bergamot, celery seeds, and sage, as well as its naturally occurring derivative perillyl alcohol, are high in limonene, a monocyclic monoterpene. The monoterpene part has been utilised successfully in malignancies of the prostate, breast, non-small cell lung, and colon because of its capacity to halt cell proliferation in the G1 phase. [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 excellent inhibitors of P-glycoprotein (P-gp) induced drug efflux, which significantly improves cancer chemotherapy by resolving multidrug resistance. [35]

Phenoxodiol

Phenoxodiol is a semisynthetic homolog of isoflavone and genistein, two naturally occurring plant secondary metabolites (2H-1-benzopyran-7-1,3-[4-hydroxyphenyl]). In a number of cancer cell lines, phenoxodiol inhibits plasma membrane electron transport and cell growth, resulting in apoptosis. Phenoxodiol is a chemosensitizer that is now being utilised in breast cancer preventive Phase-III clinical studies, as well as in the early stages of prostate and cervical cancer clinical trials. [36]

Podophyllotoxin

Podophyllotoxin is a resinous secondary metabolite found in the rhizomes and roots of Podophyllum species. The component was found 70 years after it was originally isolated from the plants Podophyllum hexandrum, Podophyllum peltatum Linn, and Podophyllum emodi Wallich in the 1880s. It comes in the form of epipodophyllotoxin, a stereoisomeric type that also acts as a substrate for the production of two physiologically active principles known as etoposide and teniposide, which are used to treat malignancies of the lymph nodes, testes, and lungs, respectively. [37]

Protopanaxadiol

Panax ginseng (Korean species) and Panax notoginseng (Chinese species) contain protopanaxadiol (PandimexTM), a tetracyclictriterpene saponin glycoside that suppresses the cell cycle via different signalling pathways, resulting in cancer cell death. Protopanaxadiol, a potent P-gp antagonist, has been shown to be helpful in the treatment of multidrug-

resistant cancers. It's also used to treat breast, colon, rectum, lung, and pancreatic cancers. According to the literature, protopanaxadiol is now conducting a Phase-I clinical study for the prevention of lung cancer and solid tumours. [38]

Salvicine

Salvicine is a new diterpenoid quinone derived from saprorthoquinone, a naturally occurring lead found in the Salvia prionitis Hance plant (Labiatae). In vitro and in vivo, salvicine exhibits strong topoisomerase-II inhibitory action against malignant tumours. [39]

Schischkinnin

Centaurea schischkinii, a member of the Asteraceae family, produces schischkinnin, a new anti-cancer indole alkaloid. Three flavonoids produced from the same plant, astragalin, afzelin, and apigenin, as well as lignin components matairesinol, matairesinoside, arctigenin, and arctiin, have demonstrated significant colon cancer involvement. [40]

Silvestrol

Silvestrol is a bioactive anti-cancer substance isolated from the twigs and fruits of Aglaia foveolata Pannell (Meliaceae). A semisynthetic epimer, episilvestrol, was recently developed, although its cytotoxicity is lower. One of the promising compounds gained popularity due to its potential to combat breast cancer, prostate cancer, and lung cancer. The plant metabolite causes apoptosis (programmed cell death) in LNCaP (hormone-dependent human prostate cancer) cells by activating caspase-2, caspase-9, and caspase-10. [41]

Taxanes

Paclitaxel (Taxol®) is a complex diterpene taxane found in the bark of the Taxaceae trees Taxus brevifoli (Himalayan yew tree) and Taxus baccata (European yew tree). Their structure was initially identified and characterised in 1971, and since the 1990s, they have been utilised to treat many types of cancer cells. Docetaxel, a water-soluble chemical, was semi-synthesised from paclitaxel, a water-insoluble, toxic molecule. Docetaxel (Taxotere®), a semi-synthetic form of paclitaxel, has been proven to be more effective in treating cervical, breast, and lung cancers, as well as colon, kidney, melanoma, esophageal, and other solid tumour malignancies, and Kaposi's sarcoma. Docetaxel and paclitaxel are both used to treat metastatic cancer, as well as breast cancer, lung cancer, cervical cancer, prostate cancer, and lymphoid malignancies. The mechanism of action is increased tubulin polymerization. Microtubules are strengthened as a consequence, and depolymerization is avoided. [42]

Triptolide

Triptolide is a diterpenoid epoxide produced from Tripterygium wilfordii Hook F, a famous Chinese medicine. This chemical moiety induces apoptosis in tumour cells, which has anticancer effects. This chemotherapeutic drug has issues with water solubility and toxicity, which are currently being solved by developing new derivatives like F60008. PG490-88 (14-succinyl triptolide sodium salt), an anti-prostate cancer derivative, is said to be in Phase-I clinical trials. [43]

Vinca alkaloids

Vincristine and vinblastine, two indole salts discovered in the Apocynaceae plant Vinca rosea or Catharanthus roseus, are potent anti-cancer chemicals. These alkaloids operate by altering microtubular dynamics during mitotic cell division, causing a distinctive block and enhanced apoptosis. Vinorelbine and vindesine, semi-synthetic analogues with a high therapeutic index, were developed and shown to have significant anti-lymphocytic leukaemia effectiveness. Anti-leukemia, anti-lymphoma, anti-advanced testicular cancer, anti-breast cancer, anti-lung cancer, and anti-sarcoma Kaposi's action has also been shown in mice. Vinflunine, a bifluorinated derivative of vinorelbine, outperforms other vinca alkaloids in terms of anti-cancer activity. In Phase-II clinical trials, novel vinca alkaloid therapeutic agents are being explored. Vinflunine and vinorelbine both have a reduced toxicity in experimental animal models. [44]

CONCLUSION

Natural ingredients have a significant role in the development of anti-cancer therapies. They provide a foundation for the creation of semi-synthetic analogues with significant tumor-suppressive potential. Because they regulate many molecular pathways, components, and targets, phytoconstituents frequently have chemopreventive effects. As a consequence, they're seen as a low-cost, easily accessible, trustworthy, and widely accepted option. Fruits and vegetables in the diet have lately been found to be chemoprotective as well as helpful against neoplasms. Lymphomas, bronchial cancer, testicular cancer, chronic myeloid leukaemia, osteocarcoma, small cell lung cancer, stomach cancer, colorectal cancer, kidney cancer, ovarian cancer, and breast cancer are among the 80 percent of cancer therapies under clinical trials that are derived from nature. This scientific study would provide an overview of phytoconstituents that may be helpful in the future for treating malignancies in a more patient-friendly way, as well as opening up new avenues for research and medication development.

CONFLICTS OF INTEREST

No conflict of interest is declared.

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