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Review Article

Phytochemical Based Nano Design for Cancer: A Recent Update

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ABSTRACT

Despite exponential advancements in medical research, various types of cancer are increasing day by day and becoming a leading cause of mortality worldwide. The worldwide cancer burden has increased to 19.3 million new cases and 10 million cancer deaths in 2020. Changes in food habits, lifestyle, different types of food additives, synthetic chemicals, environmental pollutants, different types of radiation, and limited physical activities have led to a severe increment in this disease. Healthy nutritive foods and phytochemicals play an essential role in supporting the immune system, which is beneficial in combating various types of cancer. Phytochemicals are natural bioactive non-nutrient compounds derived from various plant sources, reducing the risk of major chronic diseases. It can be easily classified and categorized into different groups based on its chemical nature and mode of biological action. These bioactive compounds are effective against various types of cancers. Recently the role of several novel phytochemicals and nanoformulations has been explored and extensively applied in cancer therapeutics. This review provides insight into various traditional phytochemicals and novel nanoformulations used in cancer management.

Keywors: Phytochemicals, Cancer, Bioactive compounds, Nano Formulation, Deficiency, Immune System.

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INTRODUCTION

Cancer is one of the world's highest causes of morbidity and mortality. The International Agency for Research on Cancer (IARC) released an updated report on the 14th of December, 2020, revealing that the global cancer burden will have risen to 19.3 million new cancer cases and 10 million deaths.[1] The IARC claims that one in every five individuals may develop any type of cancer at some point in their lifetime, with one in every eight males and one in every eleven females dying due to cancer. According to these latest Figures, more than 50 million people live within five years of a previous cancer diagnosis.

Globally, aging populations and socioeconomic risk factors continue to be the key driving force of this rise. Breast cancer (24.5%) is one of the most often diagnosed cancers in females worldwide, along with colorectal, lung, cervical, and thyroid cancers (Figure 1A). The most frequent cancers in males are lung (14.3%) and prostate (14%) cancers, which together account for approximately one-third of all cancers (Figure 1B). In the next two decades, the number of new cancer cases is estimated to rise by 70%, from 14 million to 22 million, and it is projected to continue rising by 2030 (American Cancer Society, Atlanta, USA).[1] Low- and middle-income countries have significant challenges in eradicating cancer due to limited resources available. The statistical explicit global estimates in cancer development in males and females are highlighted in Figure 1.

Cancer treatment currently uses a combination of surgical resection, radiotherapy, and chemotherapy. After chemotherapy, radiation therapy, or surgery, patients frequently experience a resurgence and malignant cell metastasis. Chemotherapeutic medicines destroy both healthy and tumour cells and long-term use leads to tumour cell resilience and significant side effects on healthy tissues and organs.[2] As a result, it is critical to employ a 'natural and safe medication' that inhibits tumour growth and targets many biological pathways in cancer cells while causing no damage in healthy cells. Furthermore, anti-cancer medicines with poor pharmacokinetic attributes due to low solubility, stability, and metabolism entail toxicity, inefficacy, and limited bio-distribution. As a result, it is critical to produce effective formulations that may solve the obstacles mentioned above while also providing selective tumour targeting without causing considerable damage to healthy tissues' viability.

Natural bioactive molecules present in vegetables, fruits, spices, cereals, and other plant products are phytochemicals.[3] Traditional medicines have long employed phytochemicals to maintain health and prevent diseases, particularly Cancer.[4-5] Many phytochemicals have been studied for cancer treatment over the last few decades all around the world. Despite the promise of phytochemicals as cancer chemotherapeutic medicines, various issues must be addressed before their use becomes commonplace. These concerns include low solubility, poor cell penetration, hepatic disposition, a narrow therapeutic index, and fast uptake by normal tissues. Meanwhile, phytochemicals have a sizeable apparent distribution volume, leading to substantial drug accumulation in healthy organs.

Furthermore, phytochemicals as therapeutics may have undesirable pharmacokinetic properties, such as a high clearance rate and a short elimination half-life. Additionally, establishing drug resistance involving numerous mechanisms is a significant barrier to the successful use of phytochemicals as cancer therapeutic agents in the treatment. The development of multidrug resistance (MDR) is another barrier to employing phytochemicals in medical care. Conventional chemotherapy is well known to be the most effective treatment for metastatic tumours. On the other hand, cancer cells might become resistant to conventional anti-cancer drugs over time, resulting in therapeutic failure.[6]

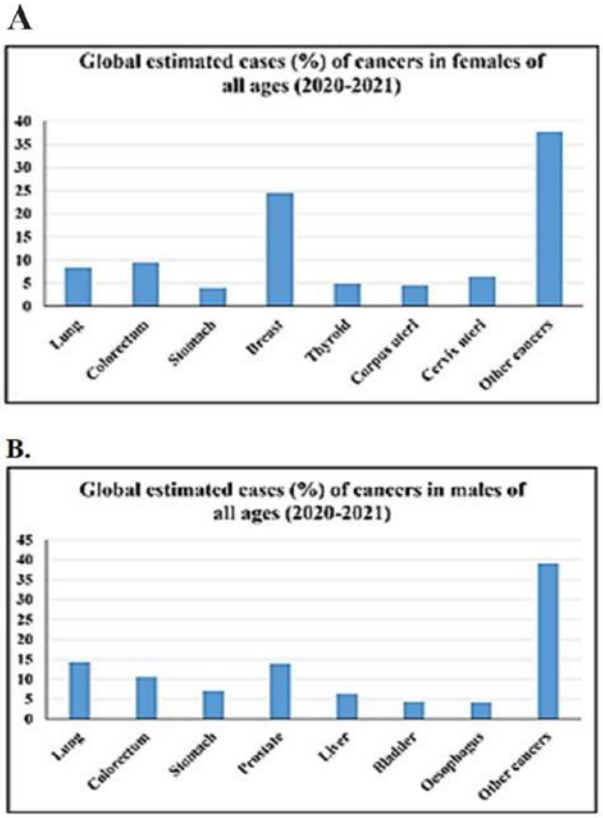

Figure 1: The worldwide estimated rate of all types of cancers in (A) females and (B) males of all age groups between 2020-2021
(Data source: Globocan-2020 Global Cancer Observatory https://gco.iarc.fr/).

PHYTOCHEMICALS USED AS ANTI-CANCER AGENTS IN DIFFERENT TYPES OF CANCERS

Plants are incredibly beneficial in the treatment of cancer. This is due to the presence of novel chemicals in many plant species that act as anti-cancer agents. In comparison to many chemotherapeutic treatments, plant-derived anti-cancer medicines have been found to have fewer side effects.[7] Herbs were once widely utilized as a treatment for various cancers in countries all over the world. According to World Health Organization reports, many countries use herbal medicine as an approved cancer treatment. Only 5–15 percent of the herbs used in cancer treatment have been studied for their anti-cancer effects.[8] 50,000 to 80,000 plants and more than this number of phytochemicals are used for various cancer therapeutic purposes worldwide (Figure 2).[9] Investigators are looking for alternative anti-cancer medicines that will limit the development of resistance induced by chemotherapies to prevent and reduce cancer occurrence.[10]

Breast Cancer

According to global data, 18.1 million new instances of breast cancer were reported in 2018, with 9.6 million fatalities. Breast cancer is responsible for up to 38.5 percent of all cancers in women. According to estimates, breast cancer will affect 43.8 million people globally in the next five years.[11] Despite the low incidence rate, the mortality rate of breast cancer in black Africans is still greater than 40%.[12]

The stromal (or supporting tissue) and glandular tissues make up most of the breast's vital tissues. The stromal tissue consists of fatty and fibrous connective tissues, whereas the glandular tissues contain lobules and

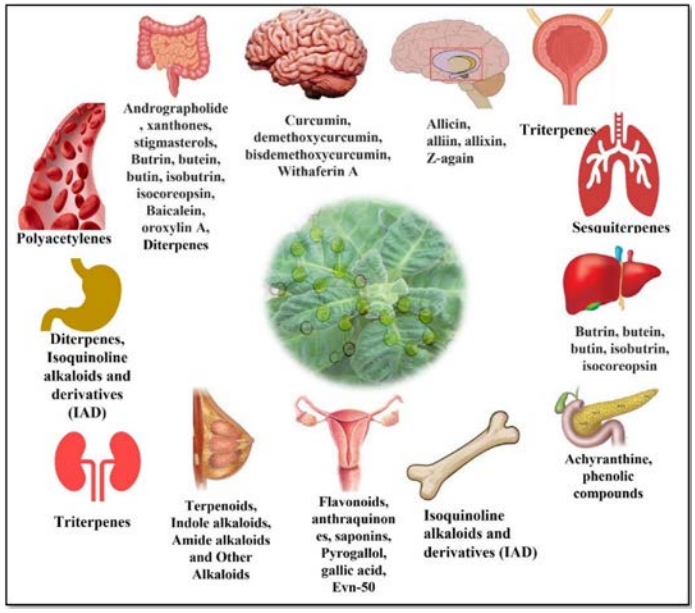

Figure 2: Phytochemicals having anti-cancer activities against different types of organ-specific cancers.

ducts. Many different types of cancers can develop in different areas of the breast. Most of them arise from the cells that line the ducts and lobules.[13] These cancers are either *in situ* or invasive. Breast carcinoma *in situ* is divided into two types: ductal carcinoma and lobular carcinoma. The forerunner of invasive cancer is ductal carcinoma *in situ*, whereas lobular carcinoma *in situ* is benign.[14]

There are several risk factors associated with the development of breast cancer. Breast cancer can be caused by several causes, including aging, family history, low parity, oestrogen, and lifestyle choices such as alcohol consumption. Clinical and theoretical studies relating to breast cancer have progressed. These studies, on the other hand, have aided in the development of breast cancer prevention strategies. Screening, biological prevention, and chemoprevention are currently used to prevent breast cancer.[15]

The stage and kind of tumour determine the treatment and management of breast cancer. Chemotherapy, surgery, human epidermal growth factor receptor 2 (HER-2) focused therapy, endocrine therapy, and radiotherapy are all standard treatment options for breast cancer.[16] The treatment of several cancers, including fgj'

rybreast cancer, has improved since the advent of natural plant-derived anti-cancer chemicals. Several studies have emphasized the advantages of organically produced phytochemicals over manufactured ones. Vitamin E, hydroxytyrosol, resveratrol, and other natural bioactive phytochemicals are commonly employed in anti-cancer therapy. Apigenin is a phytochemical found in parsley crops that has been shown to have cytotoxic effects on colon and breast cancer cell lines.[17]

Colorectal Cancer

Colorectal cancer (CRC) is the second most significant cause of cancer-related death in the United States and the third leading cause of death worldwide in both men and women. Colorectal cancer is the fourth most often diagnosed cancer, according to the 2018 GLOBOCAN study.[18] Colorectal cancer is becoming more common in industrialized countries, linked to risk factors like food, smoking, obesity, and age.[19] If caught early enough, surgery is still the most effective treatment option.[20] Plant-derived phytochemicals are increasingly being used in the treatment

and management of colorectal cancer. Natural phytochemicals prevent colorectal tumorigenesis by activating phosphoinositide 3-kinase (PI3 kinase), STAT 3, and the Wnt signalling pathway.[21]

Andrographolide, stigmasterols, and xanthones obtained from *Andrographis paniculate* show strong therapeutic ability against breast cancer cell lines and antiproliferative power against colon cancer cells (HT-29). Isoquinoline alkaloids and derivatives (IAD) from *Alangium salviifolium, Alstonia yunnanensis,* and *Aristolochia cucurbitifolia* are also used in colorectal cancer.[22-28]

Prostate Cancer

After lung cancer, prostate cancer is among the most often diagnosed cancers in men. Despite advances in cancer therapy and research, the global mortality toll from prostate cancer had grown to almost 300,000 deaths. Aging and a family genetic predisposition to prostate cancer are two risk factors for acquiring prostate cancer.[29] Prostate cancer is detected more frequently in American and European men than in other nations.[30] Apart from phytochemicals-based medication, chemotherapy, surgery, and radiation therapy are some therapeutic techniques used to treat prostate cancer.[31] Vitex negundo *derived phytochemical* Evn-50 is used for broad-spectrum cytotoxic impact on hormone-dependent and hormone-independent tumours, breast cancer, prostate cancer, and ovarian cancer.

Lung Cancer

In most nations, lung cancer is the most frequent neoplasm that affects both men and women. Lung cancer was responsible for around 27% of cancer deaths in the United States in 2015 and 20% in the European Union in 2016.[32] Tobacco use is a well-known risk factor for lung cancer, accounting for 80 percent to 90 percent of cases.[33] Various risk factors are linked to the development of lung cancer, one of which is cigarette smoking at an early age. Small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC) are the two types of lung cancer defined histologically. Even though immunotherapy has made significant progress in treating and managing lung cancer, chemotherapy remains the primary first- and second-line treatment for SCLC.[34] 6-Shogaol, a bioactive molecule derived from ginger, has been demonstrated to be helpful in the treatment of NSCLC in pre-clinical testing. 6-Shogaol reduced the growth of lung cancer cells in an experimental model employing a naked mouse. The suppression of NSCLC growth was linked to decreased proliferation and increased apoptosis induction.[35]

Isoquinoline alkaloids and derivatives (IAD) from *Alangium salviifolium, Alstonia yunnanensis, Aristolochia cucurbitifolia, Aristolochia manshuriensis, Clausena harmandiana, Goniothalamus amuyon, Macleaya macrocarpa,* and *Nauclea Orientalis* are exclusively used for Lung cancer and General treatment of cancer. Quinones obtained from *Juglans mandshurica, Rubia cordifolia* is also used in lung cancer treatment.[36-39] Alstonidine, alstonin, and Echitamine obtained from *Alstonia scholaris is* Sensitivity against human lung cancer (Table 1).[40-45]

Cervical Cancer

India is a carrier for nearly a fifth of the world's cervical cancer burden. Phytochemicals can prevent or reverse the promotion stage of multistep carcinogenesis.[46] They can also prevent or delay the transformation of pre-cancerous cells into malignant cells.[47] Plant-derived medicines such as camptothecin, taxol, combretastatin, and topotecan play essential roles in treating cervical cancer.[21] Because it inhibits topoisomerase, topotecan has been touted as a viable antitumor drug for cervical cancer.[48] Cactus pear, the fruit of the Arizona cactus, has a cytotoxic impact on human cervical cancer cells (HeLa) in aqueous extracts. In a dose and time-dependent manner, aqueous extracts of *P. oleracea* displayed anti-proliferative and apoptotic activities against a human cervical cancer cell line.[49] A well-known anti-inflammatory, antioxidant, antimicrobial, anti-diabetic, and antitumor substance, Cinnamon significantly affects cervical cancer cell development retardation. Cinnamon aqueous extract extracted from the bark of *Cinnamomum cassia* L. shows substantial anti-cancer activity against human cervical cancer cells (SiHa), influencing their growth rate in a dose-dependent fashion and inducing apoptosis via loss of mitochondrial membrane potential.[50] After 8-10 hr of incubation, polar methanol/water fractions of *Atriplex confertifolia* leaves, stems, and branches kill 90 percent of human cervical cancer cells (HeLa) but did not affect monocyte cells a control.[51]

NANOFORMULATION FOR INHIBITING CANCER PROGRESSION

The application of nanotechnology to medicine and pharmaceutical formulations, generally called nanomedicine, is revolutionizing the medical field by introducing more efficient therapeutics, medical devices, and diagnostics. Nanomedicine has the potential to revolutionize cancer diagnostic and therapeutic techniques. Novel nano-scale targeting techniques have emerged due to advances in materials science and protein engineering, improving cancer patient safety and therapeutic efficacy. Nanotechnology applies structural characterization, design, devices, production, and systems at the nanometer (nm) level. Various formulations have been established to produce nanoparticles with different compositions, size distributions, and surface properties, all of these parameters must be taken into account while creating nanoparticles for safe delivery.[52] The localization of therapy to tumour locations, drug resistance by tumors, and short drug circulation periods are significant issues with existing chemotherapeutics. Furthermore, oncogenic drug toxicity causes severe side effects such as cardiac difficulties and low white blood cell levels.

Different nanoformulations are currently available in anti-cancer medications, and they have shown to be more soluble, stable, efficacious, and have a better improved pharmacokinetic pattern, among other things. However, much care must be taken to develop effective targeted formulations that can help improve treatment outcomes while causing minimal tissue toxicity.[53-55] Numerous smart drug delivery platforms have been used for cancer treatment, including carbon-based and polymeric materials, metallic nanoparticles, and liposomes. Nanoparticles (N.P.) based nanoformulations can be employed as a drug delivery system to tumors in various ways, for instance, Liposome-mediated drug carrier (doxorubicin and daunorubicin), biodegradable and biocompatible polymeric N.P. delivery [polycaprolactone (PCL) and poly(lactic-co-glycolic acid) (PLGA)], and delivery of chemotheurepatic drugs through dendrimers [(poly-l-lysine)-octa(3-aminopropyl) silsesquioxane].[56-57] Various other innovative nanometric delivery systems for bioactive constituents have been investigated, including nanoemulsions, SLNs, nano-dispersions, and self-assembling lipidic and biopolymeric systems.[58-60] Furthermore, because human serum albumin (HSA) NPs are becoming a non-toxic drug delivery technology, their use in drug nanoencapsulation was investigated *in vitro* (human liver cancer HepG2 cells) and *in vivo* (H22 tumor-bearing mice).

Several different curcumin nanoformulations have previously been investigated in PCa cells to compare cellular uptake and cytotoxicity of materials, including -cyclodextrin (CD), hydroxypropyl methylcellulose (cellulose), magnetic N.P.s, and dendrimer-based nanoformulations. In PCa cells, the curcumin-loaded cellulose N.P.s formulation had the highest cellular absorption and generated the most apoptotic ultrastructural alterations. Second, the anti-cancer capability of the cellulose-based curcumin formulation was tested in cell culture models, and this formulation outperformed free curcumin in this regard.[61]

Recently, resveratrol nanoformulations are also used to treat certain cancers.[62] In two cancer cell lines (resistant A549/CDDP lung cells and non-resistant A549 lung cells), resveratrol nanoformulation together with dequalinium triggered cell death via the mitochondria pathway.[63] Resveratrol-loaded liposomes have been reported to have a more excellent antiproliferative activity on U-87 MG cells and suppress tumour formation in nude mice.[64] On the one hand, treatment with resveratrol nanoformulations provides numerous benefits in increased solubility, stability, oxidative inertness, and increased bioavailability. Contrarily, this route of administration must address the problems associated with nanostructure circulation in biological fluids (blood and lymph). More research is required into the safe application of nanoformulations of interest for various cancer types, including selective cytotoxicity, biocompatibility, dose, frequency of administration, and stability.

PHYTOCHEMICALS AND THEIR THERAPEUTIC POTENTIALS

Natural extracts or metabolites of plants and their resources are known as phytochemicals or phytonutrients. Secondary metabolites help manage the body's biological activities. In various disorders, polyherbal are employed as immunostimulants. Phytochemical extractives, utilized alone or in combination in Ayurvedic medicine since ancient times, are recommended. Herbal phytochemicals work by suppressing overexpressed proteins, enzymes, amino acids, and hormones, among other mechanisms. Phytochemicals also accelerate protective enzyme synthesis.

By modulating multiple pathways, phytochemicals have demonstrated antioxidant and relative oxygen generation potential. These physico-chemical properties aid immunity while not affecting healthy cells at a particular concentration. Many compounds derived from plants, such as irinotecan, marijuana, epipodophyllotoxin, and curcumin, have been shown to have anti-cancer properties. Phytochemicals, like traditional techniques, have favorable benefits in experimental studies and good clinical outcomes. Phytomedicines have been studied extensively in the past few decades as a cancer therapeutic strategy, providing an alternative to traditional medication without causing any side effects. Despite the phytochemicals' excellent promise as an anti-cancer agent, several challenges remain to be resolved. Plant-based phytochemicals have poor solubility and are extracted or separated from plants. The low solubility hampered permeability properties, which in turn hampered bioavailability. The orally administered phytoformulations may be degraded due to the first-pass effect. The phytochemicals have a narrow therapeutic range and were less specific for effective therapy.

Phytochemicals, as natural components, are easily absorbed by normal healthy tissue; they may be regarded as supplements. They are still in the research stages, and the best combination therapy is still a mystery. Phytochemicals have a large apparent volume of dispersion and can cause organ accumulation. Furthermore, the risk of acquiring resistance to phytomedicines through numerous pathways is a severe impediment to their practical use in cancer treatment. Nanotherapeutics are being used to address the shortfalls associated with traditional therapy. Indeed, nanotechnology-based phytochemical delivery offers many benefits, including passive molecule transport across a biological membrane, enhanced permeability and bioavailability, site-specific delivery, protection from biological and environmental degradation, and controlled release. Phytochemicals found in fruits and vegetables, teas, and herbal extracts help lower cancer risk when ingested.[65] Phytochemicals having anti-cancer action have been examined and categorized based on their biosynthetic origin, as illustrated in Figure 3.

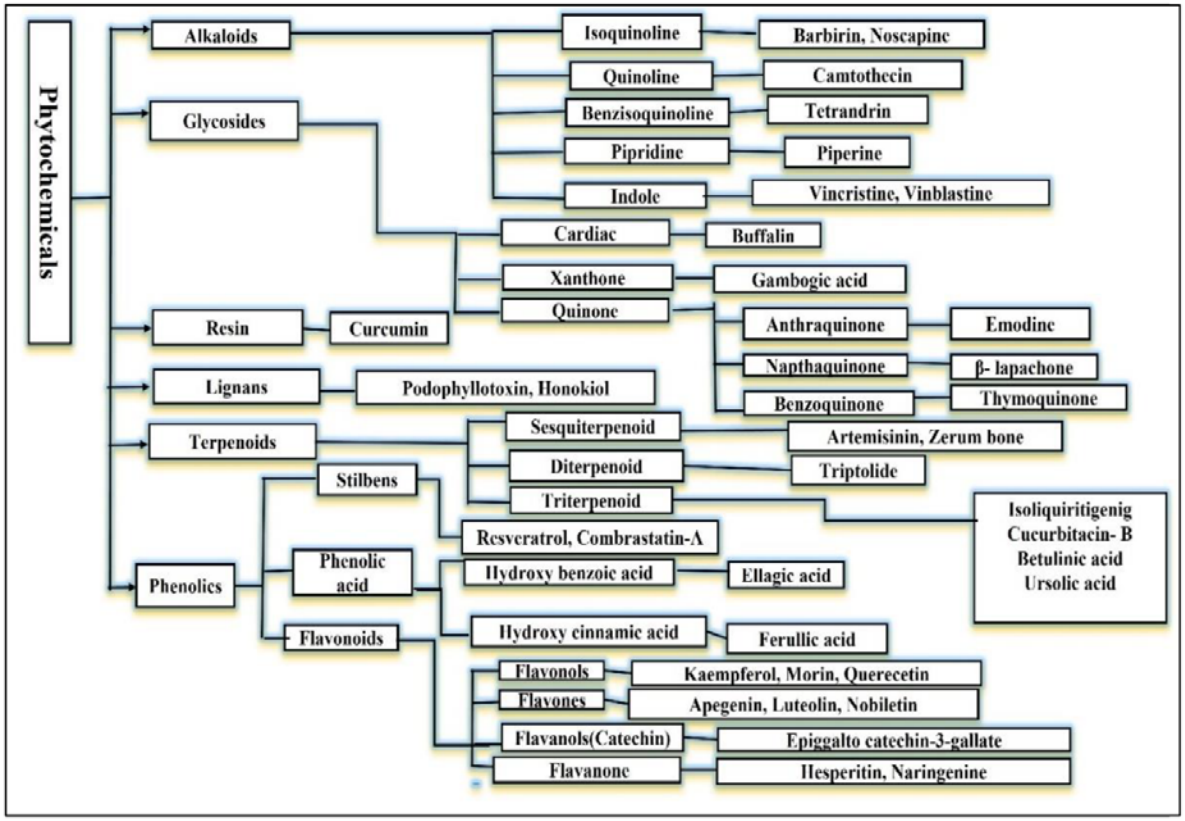

Figure 3: Classification of phytochemicals with anti-cancer potential.

Table 1: List of phytochemicals and their medicinal plants having anti-cancer properties.

Type of phytochemical	Name of Medicinal Plant	Cancer type or cell line	Reference
Isoquinoline alkaloids and derivatives (IAD)	*Alangium salviifolium, Alstonia yunnanensis, Aristolochia cucurbitifolia, Aristolochia manshuriensis, Clausena harmandiana, Goniothalamus amuyon, Macleaya macrocarpa, Nauclea orientalis*	Ehrlich ascites carcinoma, Colon cancer, liver cancer, Bone cancer, Cholangiocarcinoma, Lung cancer and General treatment of cancer	Li and Chang 1996; T.S. Wu *et al*., 2004; Deng and Qin 2010; Sichaem *et al*., 2010; Nahar and Zahan 2012; Songsiang *et al*., 2012; C. Wiart 2013
Terpenoids, Indole alkaloids, Amide alkaloids and Other Alkaloids	*Daphniphyllum glaucescens, Gynura pseudochina (L.), Piper longum, Winchia calophylla Withania somnifera*	General treatment of Cancer, Breast cancer, Dalton's ascitic lymphoma	D. Sajuthi 2001; A. J. M. Christina *et al*., 2004; L.S. Gan *et al*., 2006 ; H. Zhang *et al*., 2006; G. C. L. Ee *et al*., 2010 ; Y. Liu *et al*., 2010 ; Baig MS and Keservani RK 2016
Diterpenes	*Euphorbia fischeriana, Vitex rotundifolia*	Leukemia/myeloma; colon cancer and General treatment of cancer	G. F. Liu 1981; W. G. Ko *et al*., 2000; K.J. Jo *et al*., 2007
Triterpenes	*Alisma orientale, Brucea javanica, Dictamnus dasycarpus, Schisandra henryi*	HepG2, MDA-MB-231, MCF-7, Leukemia and HeLa cells, Bladder cancer, breast cancer	Y.G. Chen *et al*., 2003; J. Lei *et al*., 2008; A. E.Abd El-Wahab *et al*., 2013; W. Xu *et al*., 2015
Sesquiterpenes	*Atractylodes macrocephala, Ixeris chinensis, Matricaria recutita*	Lung carcinoma cells, adenocarcinoma cells, K562 leukemia cells, General treatment of cancer	T.S. Wu *et al*., 2004; L.Miao *et al*., 2011; I. Z.Mati´c *et al*., 2013
Polyacetylenes	*Apium graveolens, Petroselinum crispum*	Leukemia cell lines	C.Zidorn *et al*., 2005
Berberine	*Berberis vulgaris*	MCF-7, HepG2, and CACO-2 cell lines	A. E.Abd El-Wahab *et al*., 2013
Benzopyrones	*Hedyotis biflora*	General treatment of Cancer	X. Ding *et al*., 2014
Lignans	*Houpoea obovata*	General treatment of cancer	C. Wiart 2013
Quinones	*Juglans mandshurica, Rubia cordifolia*	P-388 cancerous cell line and Lung cancer	K. Takeya *et al*., 1993 ; J.K. Son, *et al*., 2008 ; S. Ghosh *et al*., 2010 ; Z.B. Li, *et al*., 2007
Flavonoid	*Oroxylum indicum* (L.) Kurz.	HeLa cells	D. S.Moirangthem *et al*., 2013
Rhinacanthins	*Rhinacanthus nasutus*	HeLaS3 cells	P. Siripong *et al*., 2006
Achyranthine, phenolic compounds	*Achyranthes aspera*	Antiproliferative effects against breast and cervical cancers, cytotoxic potential against pancreatic cancer	Adnyana DPA, *et al*., 2008 ; Subbarayana PR *et al*., 2010 ; Priya CL, *et al*., 2012 ; Srivastava PK. 2014; Sanghita D, *et al*. 2020
Aervitrin, aervolanine, campesterol, kaempferol	*Aerva lanata*	Induce apoptosis in MCF7 cells, antiproliferative activity against hepatic cancer cells (Hep3B)	Battu GR, and Kumar BM. 2012; Raihan O, *et al*., 2012; Bitasta M and Madan S. 2016; Govindan NK. 2016; Sanghita D, *et al*. 2020
Allicin, alliin, allixin, Z-again	*Allium sativum*	Antiproliferative actions on cancer stem cells of brain malignancies (Glioblastoma multiforme), repress colorectal, lung, and esophageal cancers	Keiss H.P. *et al*., 2003; Thomson M and Ali M. 2003; Singh VK and Singh DK. 2008; Nouroz F, *et al*., 2015 ; Sanghita D, *et al*. 2020
Alstonidine, alstonin, Echitamine	*Alstonia scholaris*	Sensitivity against human lung cancer cell lines, adenocarcinoma (MOR-P), HepG2, HL60, HeLa, K.B., MCF-7 cells, Vero cells, fibrosarcoma	Beljanski M, and Beljanski MS. 1982; Rastogi RM and Mehrotra BN. 1990; Jagetia GC and Baliga MS 2006; Jahan S, *et al*., 2009; Baliga MS. 2010; Sanghita D, *et al*. 2020
Andrographolide, stigmasterols, xanthones	*Andrographis paniculate*	Chemotherapeutic ability against breast cancer cell lines, antiproliferative power against HT-29 (colon cancer) cells, K.B. (human epidermoid carcinoma) cells, and P388 (lymphocytic leukaemia) cells,	Mishra SK *et al*., 2007; Menon V, and Bhat S. 2010; Okhuarobo A, *et al*., 2014 ;
Ludartin, lupeol	*Artemisia indica*	Strong inhibitory efficacy against MCF-7, BHY, Miapaca-2, Colo-205, and A-549 cell lines *in vitro*, as well as cytotoxicity in liver cancer cells (HepG2)	Rashid S, *et al*., 2013 ; Bayala B, *et al*., 2014 ; Zeng Y, *et al*., 2015;
Azadirachtins, azadirachtol, nimocinol, isomeldenin, nimbolide,	*Azadirachta indica*	Decrease viability of HeLa cervical cancer cells and breast cancer cells; chemotherapeutic potential in lung cancer, osteosarcoma, neuroblastoma, choriocarcinoma, leukaemia, and melanoma	Attwood E , and Joy C. 2009; Kumar GH, *et al*., 2009; Paul R, *et al*., 2011; Gupta SC, *et al*., 2017

Continued...

Table 1: List of phytochemicals and their medicinal plants having anti-cancer properties.

Type of phytochemical	Name of Medicinal Plant	Cancer type or cell line	Reference
Anthraquinones, flavonoids, saponins	*Bauhinia variegata*	Destructive potential against ovarian cancer cell lines, as well as chemopreventive action against human epithelial laryngeal carcinoma (HEp2) and human breast cancer (HBL-100) cell lines	Mali RG, *et al*., 2007 ; Mishra A, *et al*., 2013 ; Gunalan G, *et al*., 2016;
Butrin, butein, butin, isobutrin, isocoreopsin	*Butea monosperma*	Flower extracts have substantial inhibitory action on HCT-116 cells and show extraordinary effective on human colon and liver cancer cell lines	Choedon T, *et al*., 2010; Sharma AK and Deshwal N. 2011; Polachi N, *et al*., 2015 ; Subramaniyan B, *et at*., 2016;
Flavonol glycosides, gigantin, giganteol, giganteol, pregnanes, terols, usharin	*Calotrophis gigantea*	Methanol extract has antitumor action and has an anti-cancer impact on human epidermal carcinoma of the nasopharynx	Ahmed KKM, *et al*., 2005; Pardesi GS *et al*., 2008; Habib MR, and Karim MR. 2011; Kumar PS, and Kalavathy S. 2013;
Epigallocatechin-3-gallate, epigallocatechin, epicatechin-3-gallate, epicatechin	*Camellia sinensis*	Leukemia and hepatocellular carcinoma cells are inhibited from proliferating, and skin cancers are prevented from growing	Katiyar SK *et al*., 2000, Ramma AL, *et al*., 2002; Frei B and Higdon JV. 2003; Sharangi AB. 2009 ; Parmar N, *et al*., 2012; Baig MS and Keservani RK 2016;
Rhein, emodine, physion, chrysophanol, Obtusin, chrysoobtusin	*Cassia fistula*	The formation of Ehrlich ascites carcinoma, methanolic extract of seed has significant chemopreventive and tumour inhibitory action	Sen AB, and Shukia YN 1968; Gupta M, *et al*., 2000; Md. Danish, *et al*., 2011;
Asiatic acid, asiaticosside kaempferol	*Centella asiatica*	MCF-7 breast cancer cells, human melanoma SK-MEL-2 cells, and human HepG2 cell line undergo apoptosis; potent antiproliferative action in skin and lung cancer cells	Zheng CJ and Qin LP 2007; Prakash V *et al*., 2017; Hussin F *et al*., 2014; Ren L *et al*., 2016 ; Jamil SS *et al*., 2017
Curcumin, demethoxycurcumin, bisdemethoxycurcumin	*Curcuma longa* L.	Effective against melanoma, leukaemia, colon, CNS, renal, and breast cancer cell lines; suppresses the proliferation of a variety of tumour cells	Rarnsewak RS, *et al*., 2000 ; Dorai T, *et al*., 2001; Jiang J, *et al*., 2012 ; Liang G, *et al*., 2008 ; Srivastava RK *et al*., 2007
Pyrogallol, gallic acid	*Emblica officinalis*	HepG2 and H520 cell viability is reduced, while Hela (cervical), A549 (lung), MDA MB 231 (breast), SK OV3 (ovarian), and SW620 (colorectal) cell lines undergo apoptosis	Jose JK *et al*., 1997 ; Haque R, *et al*., 2001 ; Reddy VD, *et al*., 2010; Yang CJ, *et al*., 2009
Baicalein, oroxylin A	*Oroxylum indicum*	Anti-cancer potential when treated against CT-26 colon carcinoma and human breast cancer cells; cytotoxic action in MDA-MB-435S and Hep3B cell lines	Mao AA. 2002 ; Laloua C, *et al*., 2013; Kumar DRN, *et al*., 2012;
Galluflavanone, phenolic compounds	*Semecarpus anacardium*	Anti-cancer effectiveness against breast adenocarcinoma (MCF-7) and cervical epithelial carcinoma (HeLa) cell lines, as well as cytotoxic effects against acute myeloblastic leukaemia (HL-60) and chronic myelogeincleukemia (K-562)	Indap FMA, *et al*., 1983; Premalatha B. 1999; Premalatha B. 2000; Chakraborthy S *et al*., 2004; Sujatha V, Sachdanandam P. 2002
Betulinic acid, Kaempferol 7-O-methylether isoquercitin, quercetin,	*Syzygium cumini*	Pro-apoptotic capabilities against breast cancer cells; trigger apoptosis in cervical cancer cell lines- in HeLa, A2780, MCF7, PC-3, H460, and SiHa cell lines	Choi EJ, Ahn WS. 2008; Goyal PK, *et al*., 2010; Swami S.B. *et al*., 2012 ; Yadav SS, *et al*., 2011 ;
Evn-50	*Vitex negundo*	Broad spectrum cytotoxic impact on hormone dependent and hormone independent tumours; cytotoxic influence on breast cancer, prostate cancer, and ovarian cancer	Chitra V, *et al*., 2009 ; Md. Islam S, *et al*., 2013; Xin H, *et al*., 2013
Withaferin A	*Withania somnifera*	effective cytotoxicity on MCF-7, A549 and PA-1 cancer cell line; *in-vitro* cytotoxicity against A-549 (lung), PC-3 (prostrate), HCT-15 (colon), and IMR-32 (neuroblastoma) cell lines;	Nema R, *et al*., 2013; Yadav B, *et al*., 2010 ; Yang Z, *et al*., 2013 ; Rai M, *et al*., 2016

PHYTOCHEMICALS AND THEIR APPLICATION IN CANCER

Potential medicinal phytoconstituents and active components have been claimed to have anti-cancer properties since the classical era. Medicinal plants have been shown to have anti-cancer and cytotoxic properties in various researchers.[66] Polyphenols such as alkaloids, flavonoids, phenolic acids, and terpenes have medicinal plant biological potential.[67-69] Additionally, flavonoids including kaempferol, myricetin, quercetin, and rutin have also been shown to have anti-cancer effects.[67] Triterpenoids, for instance, avicins, boswellic acids, fomitellic acids, oleanolic acid, pomolic acid, and ursolic acid, have shown cytotoxic properties.[70]

Several alkaloids, including asmatrine and sanguinarine, have also been suggested to have anti-cancer properties.[71] Studies have identified possible mechanisms of action of phytochemicals and their active

components or compounds, which may act alone or in conjugation with other substances found in medicinal plants. Antioxidation is one critical potential approach of intervention for lowering disease-related damage.[72] Phytochemicals have a variety of potential anti-cancer activities, according to R.H Liu.[73] Another section examines the biological efficacies of flavonoids against cancer, particularly their potential effects.[74] Several phytochemicals found in medicinal herbs can cause cytotoxicity in cancerous cells of diverse types.

Furthermore, there has been a stronger focus on naturally occurring bioactive constituents for chemotherapy and chemoprevention in various cancers. Secondly, there has been a greater emphasis on nano therapy employing nanoformulations, which is still in its early stages of research.[55] Table 1 lists some of the plants and phytochemicals that have been found to have anti-cancer properties. Several phytochemicals, including resveratrol, have been demonstrated to have a biphasic dose-response, although an opposite biological effect characterizes this response at different concentrations, a condition is known as hormesis.[75-78] Several studies, for example, have found that resveratrol has biphasic effects on the viability and proliferation of several cell lines.[79-82]

CLASSIFICATION OF PHYTOCHEMICALS AND THEIR MECHANISM OF ACTION

Phytochemicals have shown great promise in obstructing multiple biochemical pathways involved in tumor cell survival and proliferation, directly or indirectly binding to various targets. Some of the molecular pathways through which phytochemicals may target tumour cells have been proposed. Antioxidant activity, inhibition of oncogene expression, induction of tumour suppressor gene expression, induction of cell-cycle arrest, induction of apoptosis, inhibition of signal transduction pathways, enzyme induction and enhancing detoxification, enzyme inhibition, anti-angiogenesis, inhibition of cell adhesion and invasion are just few examples. Various classes of phytochemicals and their possible mechanism of action are summarised in Table 1.

COMBINATORIAL NANOMEDICINES BASED ON PHYTOCHEMICALS

The combinatorial nanomedicines are recent development applying multifunctional nanoparticles to achieve co-delivery of chemotherapeutic agents, including proteins, small molecules drugs, and genes.[83-84] Combination chemotherapy is designed to solve some of the drawbacks of single chemotherapeutic agents, such as the development of drug resistance, significant side effects, and a limited clinical use regime. The basic principle of simultaneous administration of a chemotherapeutic drug and a phytochemical is to: (I) combine anti-cancer agents with different mechanisms of action and minimal cross-resistance to inhibit anti-cancer drug resistance; and (II) use anti-cancer agents with non-overlapping toxicities so that each anti-cancer agent can be administered near-maximal dose. The development of nanomedicines for co-encapsulation or co-delivery could offer up new avenues for cancer therapy to overcome drug resistance, reduce drug dosage, and create a synergistic or additive effect. Additional benefits could include greater patient compliance due to fewer drug administrations and lower drug doses, lowering toxicity to healthy tissues.[85-86]

CONCLUSION

Plant-derived bioactive chemicals are being regarded as a viable source of anti-cancer drugs with minimal side effects and cost-effectiveness due to rising resistance and unfavorable side effects demonstrated by radiotherapy and chemotherapy. Most countries use phytochemicals derived from plants to treat a variety of medical diseases, not just cancer. Anti-cancer, antibacterial, anti-inflammatory, antiviral, antioxidant, and antiplasmodial effects have been discovered in bioactive phytochemicals. As a result, researchers are putting more effort into investigating various plant extracts and finding the active principle chemicals. Because many anti-cancer phytochemicals lack a well-defined mechanism of action, clinical trials are required for many of them soon. Clinical trials are crucial because they aid in the validation of efficacies and side effects connected with specific drugs. One of the suggested ways to treat and manage many types of cancer for enhanced efficacy is to combine ancient medical practices with modern treatments.

Nanomaterials-based formulations have risen to the forefront of medical research as prospective cancer treatment and management strategies. The successful development of cancer nanotherapeutics requires the intelligent design and synthesis of a library of nanomaterials, precise control over their physicochemical properties, and ease of surface functionalization to boost specificity. By ensuring that healthy cells are not damaged, these techniques can limit systemic toxicity at tumor sites. Several nanoplatforms have also been designed to release cargos in response to various stimuli, allowing for multifunctionality and specificity. Despite the apparent benefits of nanotechnology-based cancer therapies, clinical translation of these nanomedicines remains a difficult task. Clinical studies face substantial failures due to a lack of understanding of nanoformulation toxicity and *in vivo* behavior. As a result, there are just a few nano-drugs currently on the market for cancer treatment. Further advances in nanomedicine, on the other hand, will lead to breakthroughs that will mark a paradigm change in cancer treatment and can considerably enhance patient outcomes. At this point, innovative design may improve materials for next-generation nanomedicine, and discoveries may deliver improved cancer management tactics.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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