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Article *in* 3 Biotech · October 2022

DOI: 10.1007/s13205-022-03372-3

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https://doi.org/10.1007/s13205-022-03372-3

REVIEW ARTICLE

Novel archetype in cancer therapeutics: exploring prospective of phytonanocarriers

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Received: 24 May 2022 / Accepted: 20 September 2022 / Published online: 15 October 2022

Abstract

This paper reports various types of cancer, their incidence, and prevalence all over the globe. Along with the discovery of novel natural drugs for cancer treatment, these present a promising option which are eco-friendly, safe, and provide better acceptability in comparison to synthetic agents that carries multiple side effects. This paper provides an idea about various nanocarriers and phytochemicals, along with how their solubility and bioavailability can be enhanced in nanocarrier system. This report combines the data from various literature available on public domain including PubMed on research articles, reviews, and along with report from various national and international sites. Specialized metabolites (polyphenols, alkaloids, and steroids etc) from medicinal plants are promising alternatives to existing drugs. Studies have suggested that the treatment of cancer using plant products could be an alternative and a safe option. Studies have shown with the several cell lines as well as animal models, that phytomolecules are important in preventing/treating cancer. Phytochemicals often outperform chemical treatments by modulating a diverse array of cellular signaling pathways, promoting cell cycle arrest, apoptosis activation, and metastatic suppression, among others. However, limited water solubility, bioavailability, and cell penetration limit their potential clinical manifestations. The development of plant extract loaded nanostructures, rendering improved specificity and efficacy at lower concentrations could prove effective. Nanocarriers, such as liposomes, nanostructured lipids, polymers, and metal nanoparticles, have been tested for the delivery of plant products with enhanced effects. Recent advances have achieved improvement in the the stability, solubility, bioavailability, circulation time, and target specificity by nanostructure-mediated delivery of phytochemicals. Nanoparticles have been considered and attempted as a novel, targeted, and safe option. Newer approaches such as phyto-nanocarriers with carbohydrates, lignin, and polymers have been considered even more selective and effective modes of drug delivery in biomedical or diagnostic applications.

Keywords Cancer · Phytochemical · Phyto-nanocarriers · Nanoparticles · Phytotherapeutics · Polyphenols · Alkaloids · Steroids · Macromolecules · Anticancer

Introduction

Cancer is a genetic disease that can be characterized by the alteration of genes. Each year, cancer ranks as the second leading cause of fatalities (Jubeen et al. 2019). Uncontrolled development and extension of the cell, due to which cell stop responding on their checkpoints, which in turn leads to growth of tumor and metastasis is known as cancer (Rai et al. 2014). It is a Non-Communicable Disease (NCD) and is widely recognized as a global threat (Christina et al. 2019). Every fourth person is at risk of their life due to cancer, which is an alarming situation (Jemal et al. 2011). A person, who is prone to cancer, has weak immunity or suppressed immune system. The factors, such as older age, stress conditions, chronic devitalizing ailments, history of chemotherapy, as well as drug resistance, all these factors may further increase the risk of cancer development (Hanahan and Weinberg 2011).

A load of cancer all over the world in 2020 is raised approximately 19.3 million new cases and about 10 million deaths. There are more than thirty types of cancer that are reported to affect both men and women, for example, breast,

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lung, liver, stomach cancer, etc. (Bray et al. 2018). Cervical cancer is one of the most prevalent cancers and a leading cause of death in women worldwide (Bray et al. 2018). The prevalence and fatality rate have risen despite recent advancements in early identification and advance therapy approaches. Nearly 7,60,000 cases of stomach cancer are identified globally, making gastric cancer (GC) the second most common cause of cancer-related deaths (Gurunathan et al. 2015). The most lethal of all female-specific reproductive malignancies is ovarian cancer. It is thought to be the sixth most common reason for cancer deaths in women worldwide, and it roughly accounts for 4% of fatalities in women worldwide. Hepatocellular carcinoma (HCC), also known as liver cancer, is one of the most frequent malignant tumors across worldwide (Anand et al. 2008). One of the most prevalent malignancies worldwide, but primarily in western countries, is colon cancer (Jemal et al. 2011). The elevated occurrences are frequently linked to diet and dietary consumption habits. A prevalent male malignancy that is spreading across the globe is prostate cancer (Almatroodi et al. 2021). With an excepted 2.3 million new cases, female breast cancer has the most commonly diagnosed malignancy. With a projected 1.8 million fatalities, lung cancer remained the largest cause of cancer mortality, followed by colorectal, liver, stomach, and female breast cancers. As per the estimate, in 2040, the world's cancer burden is anticipated to reach 28.4 million cases (Sung et al. 2021). In developed countries, like the USA, new cervical cancer cases were approx. 12,990 with 4120 deaths in the year 2016 (ACS 2016). Developing countries stand 2nd rank while developed countries stand 4th rank in cases of cervical cancer (Bray et al. 2018). The risk of cervical cancer is increased by having more full-term births, immunosuppressants (especially for HIV), smoking, oral contraceptive usage, and low socioeconomic levels, all of which are essentially causing impact on onset of disease (Bray et al. 2018). India alone contributes 25% of cervical cancer death cases among developing countries. According to the Population Cancer Registry of ICMR report, the occurrence and death were lesser in other parts of the countries compared to the northeastern region where this scale is highest (Zargar et al. 2021). Adverse medication reactions caused by chemical cancer treatments as well are substantial contributor to morbidity and mortality worldwide.

Characteristics of cancer cells

The cancer cells spread to tissues and organs outside of the site of the primary tumor through blood circulation (Jubeen et al. 2020) and may lead to the development of new tumors (Dhupal and Chowdhary 2020). Tumor cells do not depend on any growth factor, unlike the normal cell, to reach a proliferative state from a quiescent state, and also lack contact inhibition properties (Cheng et al. 2021), resulting in uncontrolled growth (Basker et al. 2010). No programmed cell death phenomenon, i.e., apoptosis (it is a kind of silent killing which does not harm nearby cells), is performed by cancerous cell (Bao et al. 2014). These cells are genetically unstable cells because of loss of gene function by mutator phenotype and oncogene-induced DNA replication stress model (Yao and Dai 2014) and do not maintain diploid chromosome complements on dividing by deletion, addition, or translocation (Cheng et al. 2021). Cancer cells are energy-hungry cells that have high metabolic requirements, so they mainly perform glycolysis. There is an enzyme known as telomerase which is responsible for maintaining the end of the chromosome that allows a cell to divide. Telomerase activity is lost in the case of normal cells (Hanahan and Weinberg 2011). The blood vessels nearby the tumor can offer a pathway for the detached cells to enter the circulatory system and metastasis to distant sites (Cheng et al. 2021); there are some characteristics as shown in Fig. 1 that may contribute to tumorigenesis and differentiate cancer cells from healthy individuals (Huynh et al. 2017).

Causes of cancer

As per an estimate and statistical analysis revealed that in developed countries, environmental and lifestyle factors are the key cause of 90–95% of cancer cases (Elisabete 2010). The lifestyle (Karikas 2010) variables include cigarette smoking (25–30% abnormalities are caused by cigarettes) (Jemal et al. 2011), diet, fried food (35% are related to food) (Boutayeb and Boutayeb 2005), red meat (Jemal et al. 2011), alcohol (Boutayeb and Boutayeb 2005; Jemal et al. 2011), sun exposure (Firdhouse and Lalitha 2015), environmental pollutants (Sunget al. 2021), infections (15–20% are related to infections) (Huynh et al. 2017), stress (Anand et al. 2008), obesity (Jemal et al. 2011), and physical inactivity (Jemal et al. 2011); overall 5–10% of all cancer cases can be attributable to genetic abnormalities, and change in cell signaling pathways (Xia et al. 2018).

Tobacco

Tobacco assigns to the development of around 20 types of cancers and has become the leading aspect of cancer globally (Sung et al. 2021). More than 70% cases of lung cancer around the globe are because of tobacco consumption (Gaziano et al. 2009). After observing the data and consequences of the health of Tobacco on people, World Health Organization (WHO) provided the Framework Convention on Tobacco Control (FCTC) in 2003. This

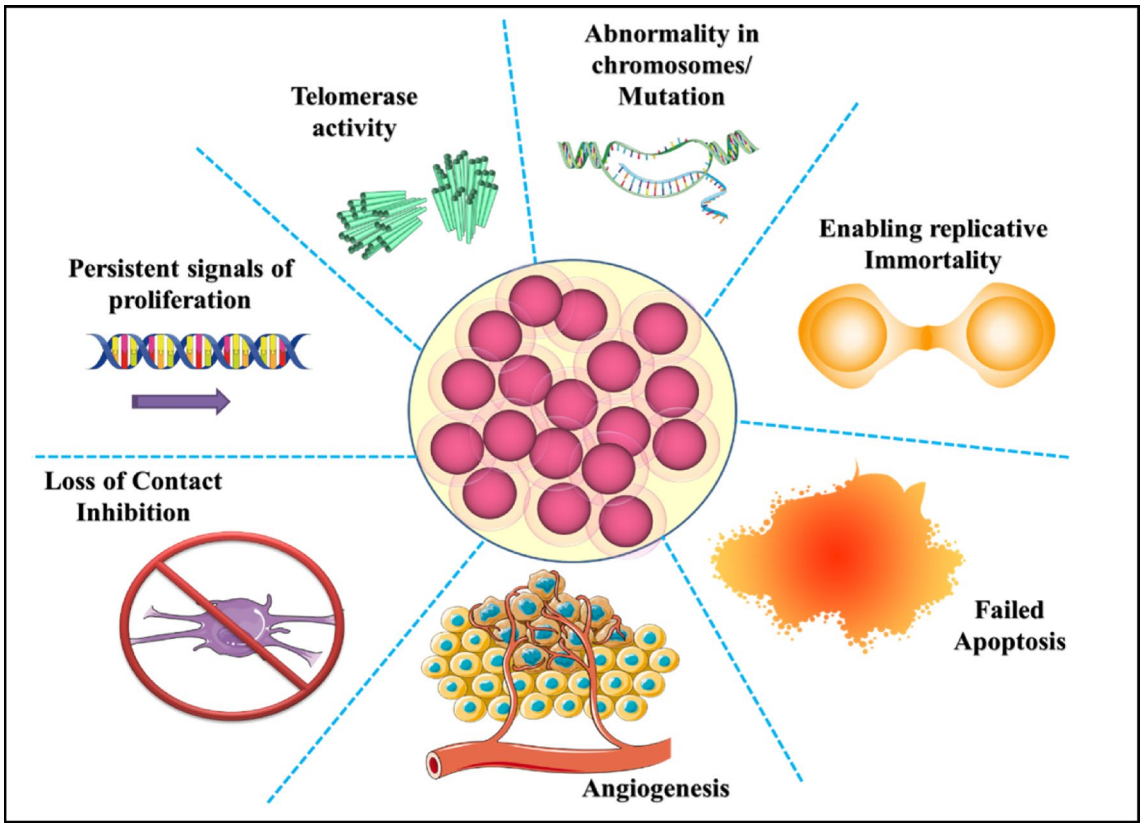

Fig. 1 Characteristics of cancerous cells

convention aimed to reduce the use of cigarettes globally, and this agreement was signed by 168 countries with control strategies on tobacco (Boutayeb and Boutayeb 2005). The first country was the USA which executed a harsh control campaign on tobacco in the 1960s, resulting in a reduction in the number of smokers (Siegel et al. 2020).

Alcohol

Chronic alcohol consumption leads to causes of certain cancer, such as aerodigestive tract, also enhanced risk of breast, hepatocellular, and colorectal cancer (Boutayeb and Boutayeb 2005). Ethanol acts as a carcinogen, and when it is metabolized, it leads to the generation of acetaldehyde and free radicals which primarily result in alcohol-associated carcinogenesis (Anand et al. 2008). The International Agency for Research on Cancer (IARC) categorized alcoholic drinks as cancer-causing agents for humans (Katzke et al. 2015). Alcohol intake is highly associated with cancer development, including mouth (Jemal et al. 2011), pharynx (Sung et al. 2021), larynx (Boutayeb and Boutayeb 2005), and esophagus (Jemal et al. 2011). Some other cancers associated with alcohol consumption are cancer of stomach, gall bladder (Katzke et al. 2015), pancreas, and lung (Gupta et al. 2016).

Diet

Carcinogens, such as nitrates, nitrosamines, pesticides, and dioxins, come from food, food additives, or cooking, those can be the causes of cancer (Boutayeb and Boutayeb 2005). Excessive intake of red meat may be correlated to colorectal, prostate, bladder, breast, gastric, pancreatic, and oral cancer (Jemal et al. 2011; Katzke et al. 2015). Nitrates and nitrites are potent carcinogens employed in meat processing as they bind to myoglobin and prevent the generation of botulinum exotoxin (Anand et al. 2008). Long-term exposure to food additives, including azo dyes and nitrite preservatives, have been linked to the development of cancer. Bisphenol from plastic food containers can also contaminate food, raising the risk of breast and prostate cancer (Srikrishna and Sachsenmeier 2021). Most trans fatty acids, processed sugars, refined wheat, saturated and unsaturated fatty acids foods have been linked to cancer (Katzke et al. 2015; Anand et al. 2008).

Obesity

Overweight and obesity are considered as more common cause over the world than ever before-in adults (by about 27%, and in children by about 47%). When caloric intake exceeds and energy spent decreases through metabolism and physical exercise, obesity sets in. Fat is deposited and accumulated as ectopic fat in tissues as a result of excessive or aberrant fat tissue formation that surpasses the genetically and epigenetically specified adipose tissue reserves, increasing the risk for numerous diseases, including cancer (Avgerinos et al. 2019). According to American Society study, obesity is linked to enhanced mortality cases among various cancer types, such as colon (Jemal et al. 2011), breast, endometrium (Boutayeb and Boutayeb 2005), kidney (Jemal et al. 2011), esophagus (Jemal et al. 2011), gastric, pancreas (Boutayeb and Boutayeb 2005), prostate (Boutayeb and Boutayeb 2005), gallbladder (Anand et al. 2008), and liver cancer (Katzke et al. 2015). A relative risk of more than 1.5/5 kg/m^2 enhances the BMI and was reported in esophageal cancer for both males and females (Katzke et al. 2015).

Infectious agents

Viruses are one of the main source of cancer caused by infection. The infection caused by *Helicobacter pylori* is a relevant illustration of the inflammatory process of carcinogenesis (Gurunathan et al. 2015). About two-thirds of people on the planet have the stomach infection caused by *H. pylori* bacteria. *Fusobacterium nucleatum* influences the tumor immune microenvironment and encourages the development of intestinal and colorectal tumors (Gurunathan et al. 2015). Other viruses which are associated with various types of cancer are the Human T-lymphotropic virus, Herpes, heaptitis B and HIV virus (Jemal et al. 2011), and Hepatitis C virus (Anand et al. 2008). These agents cause more harm to the people who are deficient of antioxidants and antioxidant nutrients taken from fresh fruits and vegetables (Gupta et al. 2016). HBV and HCV viruses generate reactive oxygen species by chronic inflammation as well as activate NF-kB (Nuclear Factor Kappa B) an inflammatory marker and lead to mutagenesis (Anand et al. 2008).

Environmental pollution

This aspect includes both outdoor as well as indoor pollution (Sung et al. 2021). Outdoor pollution may be caused by various pollutants including Polycyclic Aromatic Hydrocarbons (PAHs), nitric oxide, and motor vehicle exhaust, while indoor pollution might be caused by tobacco smoke formaldehyde, volatile organic compounds, food additives, nitrates, pesticides, dioxins, metals, metalloids, pharmaceuticals medicines, and cosmetics etc (Sung et al. 2021). All of these pollutants are reported to enhance the risk of leukemia, lymphoma, testicular, colorectal (Anand et al. 2008), bladder, brain tumor (Firdhouse and Lalitha 2015).

Radiation

Cancer has been reported to be caused by both ionizing (X-ray, gamma rays) and non-ionizing radiations (UV, IR, microwaves). These might be involved in enhanced cases of leukemia, lymphoma, thyroid (Sung et al. 2021), skin, sarcoma, lung, and breast cancers (Anand et al. 2008). UV radiations have also been reported to be the more common cause of lip cancer specifically for lower lips (Gupta et al. 2016).

Abruption of cell signaling pathways

The cell signaling process is the way by which a cell responds to external signaling molecules that bind to receptors on the cell membrane or in the cytoplasm of cells (Nair et al. 2019). The binding of receptors sends signals to the nucleus, where they are translated into gene expression, resulting in biological effects and cellular responses. Signaling pathways are less tightly controlled during carcinogenesis. Cancer is characterized by abnormal regulation and cross-talk of cell signal transduction pathways (Khan et al. 2019a), and obstruction of or anomalies in signaling pathways can lead to excessive cell proliferation (Huynh et al. 2017), apoptotic resistance, angiogenesis, invasion, and metastasis (Huynh et al. 2017), all of which contribute to cancer development and progression (Xia et al. 2018). Aberrant Rat Sarcoma Virus "RAS" protein activation (family of related proteins that shows expression in all the animal cells lineage and organs), the principal oncogenic operator that controls the functioning of important signaling pathways involved in the onset (Khan et al. 2019a) and development of human malignancies is abnormally activated RAS proteins (Nair et al. 2019). RAS gene mutation, which are most common in human malignancies, are the primary cause of persistent RAS activation and associated pathological diseases, such as cancer (Huynh et al. 2017). RAS is the key upstream regulator of several highly conserved signaling systems linked to a variety of important cellular processes that are required for appropriate homeostasis (Khan et al. 2019a) (Fig. 2). Mutated or oncogenic RAS activates a complexly interlinked signaling pathway, such as Mitogen-Activated Protein Kinases (MAPK) (Murthy et al. 2018), Phosphatidylinositol-3-Kinase (PI3K)/Akt pathways (Chamcheu et al. 2019), Protein Kinase C (PKC), and Ral Guanine Nucleotide Dissociation Stimulator (RalGDS), among others, resulting in uncontrolled transcriptional expression and reprogramming in the functioning of a range of nuclear and cytosolic effectors critically associated with the hallmarks

of carcinogenesis (Khan et al. 2019a). The PI3K/Akt is a survival pathway and deregulation in this signaling pathway leads to malignancy. This pathway is a hub involved in a variety of physiologic functions linking growth factors nutrients, energy availability to lipid and protein synthesis, metabolism, cell growth, survival, apoptosis, angiogenesis, and tissue development (Nair et al. 2019). Disruption of these pathways leads to variety of malignancies, such as melanoma and non-melanoma skin tumors, and is emerging as clinically important therapeutic targets (Chamcheu et al. 2019). Signal Transducer and Activator of Transcription 3 (STAT3) signaling in tumor cells are important for cell proliferation and survival, and it also regulates many activities in the non-transformed cells that make up the tumor microenvironment. As a result, increased STAT3 activation is a characteristic of many cancers, and it happens frequently in response to cytokines from the Interleukin (IL-6 and IL-10) families (these are proinflammatory cytokines) (Haura et al. 2005), on the other hand, regulates the effector's function of tumor-associated immune and stromal cells, which help tumors grow by inhibiting the host's antitumor immune response (Wang et al. 2018). The molecular actors of STAT3 signaling and its upstream JAK kinases represent feasible therapeutic targets for the treatment of cancer since STAT3 mediates tumorigenic effects in a variety of cell types (Huynh et al. 2017).

Cancer management

There have been several treatment plans and medications for the management of cancer. However, none of them are delivering results that are adequate to full satisfaction (Jubeen et al. 2019). Chemoprevention is a method to prevent or avoid chronic degenerative diseases by using natural or artificial agents. Chemopreventive components are those components that can cease cancer furtherance and progression or perhaps also target at the stage of initiation of carcinogenesis itself (Fimognari et al. 2012). Chemically synthesized drugs have not significantly improved the overall survival rate over the past decades (Choudhari et al. 2020). These target a particular pathway through a specific mechanism. These medications may adversely damage the body's organs and may cause renotoxicity, hepatotoxicity, and other undesirable consequences (Ashrafizadeh et al. 2020). The main drawback of chemotherapy includes cancer recurrence, drug resistance, and very harmful effects on tissues that are not being treated easily which might limit the use of anticancer medications and reduce the quality of life of patients (Choudhari et al. 2020). The naturally occurring bioactive compounds are of more interest to researchers because they can affect a wide range of molecular signaling pathways and reduce associated side effects (Yadav and

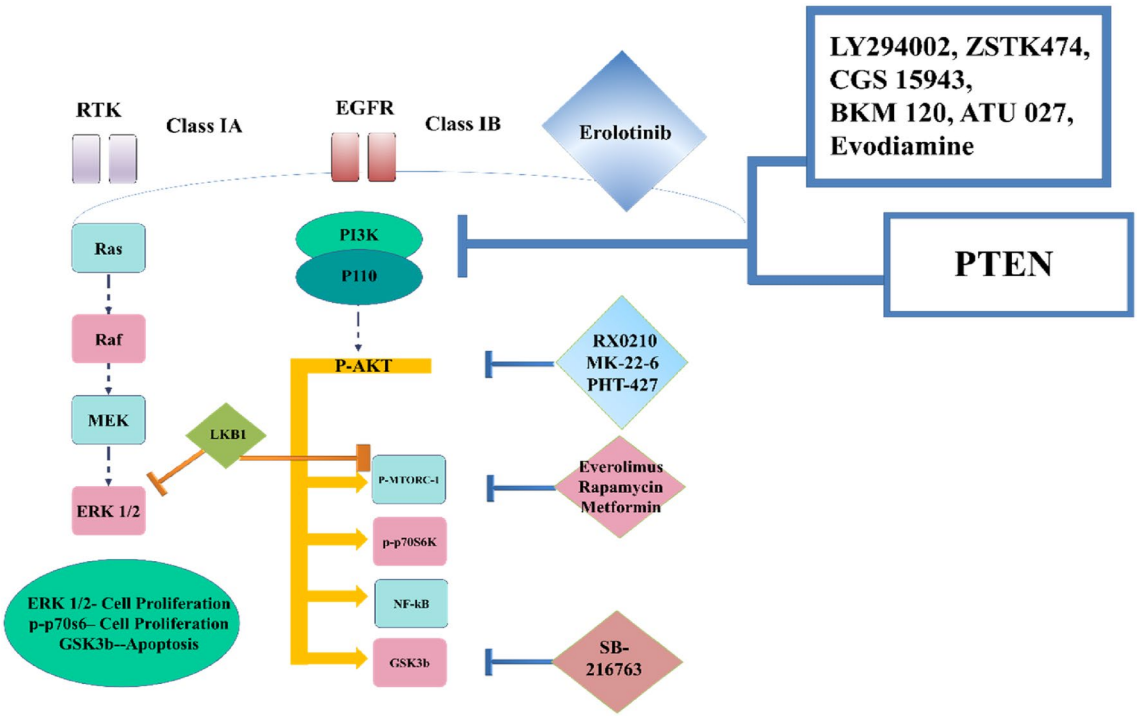

Fig. 2 The PI3K/Akt survival pathway is a critical downstream target of the rat sarcoma virus (Ras) family of proteins, largely involved in cell proliferation. De-regulation of the PI3K/Akt signaling pathway is thought to affect at least 50% of all cancer patients and 60% of all PDAC patients (Murthy et al. 2018)

Sangwan 2022; Diwan et al. 2021; Ashrafizadeh et al. 2020). The multi-targeting properties of herbal substances have sparked a lot of interest (Yadav and Sangwan 2022; Sharma and Sangwan 2022). A large amount of structural diversity in natural compounds exists because of molecular modifications which provide added advantage of an improvement in therapeutics (Srivastava and Sangwan 2020; Karikas 2010).

Cancer management using plant products

Compounds' various actions are caused by certain structural characteristics. Numerous naturally occurring chemicals, including antibiotics, vitamins, plant products, and nucleic acids, include heterocyclic compositions with nitrogen as essential building blocks have been used for various purposes. Since its discovery in 1957, 5-fluorouracil (5-FU), an antimetabolite of pyrimidine and a commonly used anticancer medication, has been the subject of much research. The derivatives of 5-FU molecules of the enone functional group are related to many other naturally occurring molecules, which are known for their significant antiproliferative and anticancer properties (Jubeen et al. 2019). Non-targeted cytotoxicity and other health-related problems, such as alopecia, vomiting, and diarrhea, are linked to downside with 5-FU treatment, whether intravenously, orally, or topically (Jubeen et al. 2019). There is a requirement for novel therapeutic agents to reduce these challenges (Maqsood et al. 2021). Phytochemical have received a lot of attention for their possible role in cancer prevention (Elangovan et al. 2015). Selected phytochemicals have exhibited anticancer properties in a variety of studies and some have in clinical trials. Several chemical entities of secondary plant metabolites, microbial metabolites, peptides plant alkaloids, flavonoids, terpenoids, steroids, flavonolignans, and organosulfur compounds (Diwan et al. 2021; Greenwell and Rahman 2015), have been discovered, isolated, described, and clinically tested for their potential to treat cancer (Dhupal and Chowdhury 2020). Herbal chemicals have been shown to have low or even no toxicity to normal cells in addition to having beneficial properties, like enhancing antioxidant status, inactivation of carcinogens, halting growth, as well as induction of cell cycle arrest and programmed cell death (Choudhari et al. 2020). All of these observations support the idea that the herbal chemicals are relative safe and more effective disease-treating agents and that they may be used to target different biochemical pathways (Ashrafizadeh et al. 2020).

Cruciferous vegetables, i.e., *Brassicaceae* families of plants, have abundant economic significance and have around 340 genera, 3700 species. Valuable metabolites present in vegetable *Brassica* were found to be very effective in cancer chemoprevention and reduce various types of cancers, such as prostate, renal, colorectal, lung, breast, and oral cancer because they contain vitamins C and E, carotenoids (Avato and Argentieri 2015), and antioxidant enzymes, like Superoxide Dismutase (SOD), catalase (Gaziano et al. 2009), polyphenols (Sharma et al. 2018b), peroxidase, and sulfur organic compounds (Mandrich and Caputo 2020). Moreover, these greens are enriched with unstable compound glucosinolates, which convert into biologically active compounds indoles and isothiocyanates under the effect of the myrosinase enzyme, present in plant tissues (Mandrich and Caputo 2020). These components via xenobiotic metabolism instruction may result in neutralization or removal of carcinogenic as well as mutagenic factors which further inhibit the process of DNA methylation and progression of tumor (Kapusta-Duch 2012).

Dietary supplements which are herbal plant products under Dietary Supplement Health and Education Act (DSHEA) are utilized being part of their supportive health practices (Clarke et al. 2015). Dietary supplements are mostly used by cancer patients in comparison with healthy individuals.

Plant products are reported to inhibit various cancers (Table 1). A phytochemical-rich diet decreases the risk of cancer substantially depending upon the enriched diet. Phytochemicals play a significant role in the formulation of drugs; the use of these phytochemicals can be an effective strategy as it conquers mortality with a frightening rate of 1.6 million deaths every year. Early reports have proved that various phytochemicals possess powerful reactive oxygen species scavenging vehicles for lung cancer. Plant secondary metabolites in vitro have been demonstrated to have powerful cytotoxic effects against malignant cells of liver (Wang et al. 2013), colon (Baskar et al. 2010), lung (Li et al. 2013), ovarian (Moghadamtousi et al. 2014), cervical, and neuroblastoma (Sharma et al. 2018b). Various types of phytochemicals, their occurrence and effectiveness are as follows:

Polyphenols

Polyphenols, which are natural antioxidants, are considered to boost health and lower the cancer risk when included in diet (Greenwell and Rahman 2015). They are secondary metabolites generated by plants that have a large number of phenolic rings in them. Berries, grapes, olive oil, chocolate, almonds, peanuts, and other fruits and vegetables are high in polyphenols, including up to 300 mg/100 g fresh weight (Sharma et al. 2018b). Polyphenols are also found in substantial levels of goods made from these fruits, such as tea, wine, berries, and beer (Turan et al. 2017). The amount and features of phenolic groups determine the specific qualities of each polyphenol class. They have a variety of roles in plants, including several that are required for plant physiological processes (Khan et al. 2020). These assist in the defense of the body against various kinds of stress and other

Table 1 In vivo and in vitro anticancer activities of medicinal plants and their active constituents

Plant's name	Common name	Parts utilized	Tested on cancer cell lines	Animal Models	References
Allium sativum	Garlic	Leaves	WEHI 164 cells	Balb/c mice	Shirzad et al. (2011)
Alpinia galanga	Lengkuas, blue ginger	Rhizomes	DLA and A549 cells	Balb/c mice	Lakshmi et al. (2019)
Alstonia scholaris	Blackboard	Stem bark	HeLa cells	Mice	Mondal et al. (2012)
Andrographis paniculata	Green chiretta	Aerial parts	SW620 and A-498 cells	Swiss Albino mice	Khan et al. (2020)
Angelica archangelica	Wild celery	Root and rhizome	MCF-7 and 4T1 cells	Balb/c Mice Female	Oliveira et al. (2019)
Aralia elata	Japanese angelica tree	Leaves	MCF-7 cells	Tumor Bearing-nude Mice	Li et al. (2019)
Asclepias curassavica	Tropical milkweed	Shade dried leaves	COLO320 DM cells	Wistar male rats	Baskar et al. (2010)
Brassica napus	Mustard	Roots and leaves	Renal, prostate, oral, colorectal lung, and breast cancer	–	Thomson et al. (2010)
Copaifera multijuga	Hayne oil	Tree trunk	B16-F10 cells	MaleC57/black Mice	Carneiro et al. (2020)
Coptidis rhizoma	Huanglian, Copaiba	Root	HepG2 and MHC97-1 cells	–	Wang et al. (2010)
Curcuma longa	Turmeric	Rhizome	Ht-29 cells	–	Khan et al. (2020)
Elephantopus scaber	Elephants Foot	Whole plant	EAC cells	Swiss male albino mice	Kabeer et al. (2019)
Garcinia indica	Kokum	Fruits	HCT-116 andHT -29 cells	–	Khan et al. (2020)
Garcinia oblongifolia	Lingnan garcinia	Branch	MCF -7 cells	–	Li et al. (2016)
Hedyotis diffusa	White flower Snake-tongue grass		HeLa cells	Nude xenograft mice	Li et al. (2012)
Kaempferia parviflora	Black ginger	Rhizomes	SKOV3 cells	–	Paramee et al. (2018)
Loranthus parasiticus	Mulberry Mistletoe	Leaves	SKOV-3, CAOV-3, OVCAR-3 cells	Rat	Moghadamtousi et al. (2014)
Menyanthes trifoliata	Bogbean, Buckbean	Aerial part and root	Grade IV glioma cells	–	Kowalczyk et al. (2019)
Morus alba	white mulberry	Root	HL-60 and CRL-1579 cells	–	Kikuchi et al. (2010)
Morus nigra	Blackberry	Airy portion	PC-3 cells	–	Turan et al. (2017)
Nitraria retusa	Salt tree	Leaves	B16-F10 cells	Balb/c mice	Boubaker et al. (2018)
Paris polyphylla	Herb Paris	Rhizomes	A549 cells	c57bl/6mice	Li et al. (2013)
Perilla frutescens	Beefsteak plant	Leaves	Huh-7 cells	Tumor nude xenograft mice	Wang et al. (2013
Prunus armeniaca	Apricot	Fruit, seeds	HCT116, MCF-7 andHep G2 cells	Rat	Gomaa (2013)
Platycodon grandiflorus	Balloon flower	Root	MCF-7 cells	–	Yu et al. (2010)
Rabdosia rubescens	Bing Ling	Whole plant	SGC-996 andNOZ cells	Nude athymic Mice	Bao et al. (2014)
Rhizoma curcumae	Turmeric	Rhizome	JF- 305 andMCF-7cells	Tropical fish	Zhu et al. (2019)
Scutellaria barbata	Barbed Skullcap	Whole plant	95-D cells	Xenograft	Yang et al. (2014)
Scutellaria baicalensis	Baikal skullcap	Root	OSCC cells	–	Sato et al. (2013)
Tussilago farfara	Coltsfoot	Flower buds	HT-29 cells	–	Lee et al. (2014)
Withania somnifera	Ashwagandha	Leaves, roots, stem and flower	MCF-7 (breast), WRL-68 (liver), PC-3 (prostate) and CACO-2	–	Siddique et al. (2014) Srivastava and Sangwan (2020)

Table 1 (continued)

Plant's name	Common name	Parts utilized	Tested on cancer cell lines	Animal Models	References
Wedelia chinensis	Chinese Wedelia	Leaves	B16-F10 cells	C57bl/6 mice	Manjamalai and Grace (2012)

environmental stimuli (Montane et al. 2020). *Azadirachta indica* is a medicinal tree studied for its various phytochemicals including gallic acid, caffeic acid, tannic acid, chlorogenic acid, ferulic acid, quinones, kaempferol, epicatechin, quercetin, hydroquinone, 4-caffeoyl quinic acid, and protocatechuic acid having anticarcinogenic properties (Narnoliya et al. 2021; Sharma et al. 2018b).

Stilbenes These are hydroxylated derivative compounds produced from several plants, including strawberries, grapes, peanuts, and cannabis (Amarowicz and Pegg 2019). Resveratrol (3,5,4′-trihydroxy-trans-stilbene) a natural polyphenol, present in a variety of foods, such as peanuts, grapes, and red wines, has been identified as a possible anticancer treatment in recent studies (Ren et al. 2021). It inhibits tumor growth and reduces metastatic potential by preventing tumor initiation, and acts as antimutagen to reduce tumor promotion. Stilbenes affect several signaling pathways, including the insulin-like growth factor system (Ko et al. 2017), (Wingless-Related Integration Site) Wnt signaling (Lohse et al. 2018), Notch-1 signaling, STAT3 (Signal Transducers and Activators of Transcription 3), the Akt/mTOR (Mammalian Target of Rapamycin Pathway), and Sirt1/MAPK (Mitogen-Activated Protein Kinase Pathway) (Lohse et al. 2018). They suppressed the expression of β-catenin, an important component of Wnt signaling. The expression of β-catenin, a protein required for the canonical Wnt signaling pathway, was down-regulated by resveratrol. Another research discovered that the STAT-1, Notch-1, and Wnt signaling pathways in cervical cancer cells are found to be suppressed by resveratrol (Zhang et al. 2014). Resveratrol was also discovered to promote apoptosis via blocking the Akt/mTOR pathways and up-regulating the p38-MAPK in a different investigation employing on T-cell leukemia cells (Ge et al. 2013). Yet another study pointed toward the Sirt/AMPK pathway as a potential target of resveratrol (Ko et al. 2017). Because of its therapeutic effects resveratrol affects so many various pathways and have so many possible interactions (Lohse et al. 2018).

Curcuminoids Curcumin is a natural polyphenol curcuminoid, extracted from *Curcuma longa* rhizomes, having an antineoplastic activity (Lohse et al. 2018). Mainly, dietary foods, i.e., curries made with ginger and turmeric, are rich in curcumin. Curcumin is referred in studies to treat various types cancer, including pancreatic, breast, bone, liver, lung, cervix, and prostate (Dhupal and Chowdhary 2020). Curcumin affects a variety of cellular signaling pathways and has a wide range of targets. WNT/β-catenin (Ashrafizadeh et al. 2020), NOTCH, (Transforming Growth Factor) TGF/Smads (Ashrafizadeh et al. 2020), SHH, STAT3 (Huyanh et al. 2017), PI3K/AKT (Ashrafizadeh et al. 2020), and NF-κB/COX-2 signaling pathways are among them, and they play essential roles in cancer formation and progression (Sultana et al. 2021). Curcumin in vitro causes apoptosis and inhibits cell growth and invasion in pancreatic cancer cells in vivo by decreasing tumor development and angiogenesis. Curcumin therapy also reduces NF-κB binding and IkappaB kinase activity. This change was linked to a time-dependent decrease in cancer cell proliferation and an increase in apoptosis by increase in FOXO1 (Forkhead Box-Protein O 1) expression (Sultana et al. 2021). Dimethoxy curcumin is a curcumin derivative utilized in the treatment of breast and kidney cancer (Yallapu et al. 2013). Other studies also demonstrated that curcumin derivatives can be effective in the treatment of colon cancer cells by lowering surviving expression and increasing E-cadherin, a cell adhesion protein whose loss contributes to the development of epithelial tumors (Montane et al. 2020).

Flavonoids A group of polyphenols consists of more than 6000 molecules. They are present in green vegetables and other colored fruits, including apples, strawberries, blueberries, plums (Turan et al. 2017), grapes (Sharma et al. 2018a, b), and oranges (Montane et al. 2020). *Camellia sinensis* isolated polyphenol, Epigallocatechin Gallate (EGCG), and *Vinca rosea* isolate vinorelbine tartrate were found to have formidable antineoplastic activity as compared to various cancers thus exhibited therapeutics potential (Dhupal and Chowdhury 2020). Acacetin a flavonoid of the Fabaceae family possibly inhibits the proliferation of A549 cell lines as well as enhances protein p53 and p21, which leads to apoptosis activation and arrest of the cell cycle. *Glycine max* soy isoflavones was reported to possess antineoplastic activity to cure cancer cases (Dhupal and Chowdhury 2020). *Dysoxylum binectariferum* extract alvocidib which is flavopiridol was found to activate apoptosis through inhibiting CDK9 with CDKs (Cyclin-Dependent Kinases), stopping phosphorylation, and cause cell cycle arrest at the G1 phase (Zocchi et al. 2018). In MDA-MB-231 cancer cells, kaempferol a natural flavonol cause apoptosis and DNA damage by upregulating the phosphorylated version of the H2A His-

tone Family Member X (H2AX), caspase 3, caspase 9, and the protein serine/threonine kinase (p-ATM) (Baharara et al. 2015).

Alkaloids

These natural products are present in almost all plants specifically in the specific blooming plants family.

Camptothecin analog Topotecan drug (topoisomerase-1 inhibitor) extracted from *Camptotheca acuminate* tree was approved by FDA for nursing cervical, small cell lung, and ovarian cancer. *Vinca rosea* (Dhupal and Chowdhury 2020) alkaloid extract vincristine sulfate arrests tumor cell in S phase and M phase of cell cycle, which is named as Oncovin approved by FDA, given to leukemias patient, lymphoblastic lymphoma, Philadelphia Chromosome-Negative (Ph-) Acute Lymphoblastic Leukemia (ALL), Burkitt lymphoma, and solid tumors of all groups. Vinorelbine is also accepted by FDA as the brand name Navelbine for treating advanced gastroesophageal adenocarcinoma, small lung cancer (Zhang et al. 2020), breast, human hepatocarcinoma (Huyanh et al. 2017), and human colon cancer when used in combinational therapy (Dhupal and Chowdhury 2020).

Arctigenin is isolated from seeds of *Arctium lappa* causing senescence in gallbladder cancer tissue by the down-regulating expression level of Epidermal Growth Factor Receptor (EGFR) by enhancing Fibrosarcoma (RAF)–Mitogen-Activated Protein Kinase (MEK)–Extracellular-Regulated Kinase (ERK) signaling pathway. It leads to cell cycle arrest at G1/G0 phase via decreasing expression of EGFR and causes apoptosis (Mondal et al. 2019).

Vincristine, vinblastine, and vindesine compounds were isolated from the *Catharanthus roseus* plant belonging to the Apocynaceae family and have anticancer effects used to treat various types of cancer, including lymphomas, leukemias (Choudhari et al. 2020), breast, lung cancer (Devaraj et al. 2014), advanced testicular, and Kaposi's sarcoma (Mondal et al. 2019).

Glycine max isolates phytoestrogen, isoflavone, and genistein have antineoplastic properties. It has topoisomerase-II and protein-tyrosine kinase inhibition activity, which leads to cell cycle arrest at the G2/M phase along with activation of apoptosis. It is also used for treating early-stage prostate cancer (phase II), metastatic colorectal cancer (phase I/II), and stage IV breast cancer (phase II) under different clinical trials (Dhupal and Chowdhury 2020).

Steroids

Withania somnifera is a rich source of steroids withanolide having unique pharmacological properties, including anticancer (Sangwan et al. 2017). Several withanolidal moieties have proven to be useful candidate in prostate cancer via activating cell cycle arrest, apoptosis, and autophagy along with inhibition of different cancer-causing pathways (Ramakanth et al. 2016; Sangwan and Sangwan 2014; Srivastava and Sangwan 2020).

Cancer management using biological macromolecules

Tetrapyrrolic macrocycles, including porphyrins, chlorins, bacteriochlorins, and phthalocyanines are among the photosensitizers (PS) being studied for cancer therapy. Porphyrin compounds with pharmaceutical activity imitate photosynthetic centers, P-450, and vitamin B12. Porphyrins are a new chemotype that might be used to treat cancer. Porfimer sodium was the first PS to be approved by the FDA in clinical trials for bladder cancer, while verteporfin and phthalocyanines are now being tested. It does, however, have significant drawbacks, such as hydrophobicity, target specificity, long-term skin photosensitivity, and a lack of absorption at longer wavelengths (Diwan et al. 2021; Kirar et al. 2021).

Multidrug-Resistant (MDR) infections have been successfully treated with synthetic macromolecular antimicrobials. Antimicrobial Peptides (AMPs) are synthetic macromolecules that damage microbial cell membranes or target several intracellular proteins or genes to reduce resistance (Tan et al. 2020). AMPs can be utilized as anticancer treatments, according to recent research. The use of AMPs as anticancer medicines has been motivated by the never-ending search for new anticancer drugs known as Anticancer Peptides (ACPs) (Mader et al. 2006).

ACPs, which typically include 5–50 amino acid residues, frequently acquire secondary structures, like α-helical or β-sheets. They also have various distinct physical characteristics, such as strong cationic charges and hydrophobicity, that aid in the development of amphiphilic complexes and improve their interactions with cancer cells. ACPs killed cancer cells by including apoptosis, necrosis, or a combination of two (Tan et al. 2020).

A series of research look into the possibility of using polymer–drug conjugates to improve conventional chemotherapy. Anticancer therapies, such as paclitaxel, doxorubicin, camptothecin, and peptides, were delivered to solid tumors using polymers, such as styrene–maleic acid, Polyethylene Glycol (PEG), poly(l-glutamic acid), and poly[*N*-(2-hydroxypyropyl)methacrylamide] (MacEwan et al. 2010). When doxorubicin was conjugated to poly[*N*-(2-hydroxypropyl)methacrylamide], it increased circulation and tumor accumulation, resulting in greater anticancer activity relative to the free drug (Yallapu et al. 2013). In melanoma, colon, and lung tumors, camptothecin conjugated to poly(l-glutamic acid) had higher anticancer activity than the free drug, with increased drug loading and a higher polymer molecular weight boosting this activity. In comparison to

free medication, dendrimers conjugated with doxorubicin and camptothecin showed better pharmacokinetics, biodistribution, and antitumor effectiveness (MacEwan et al. 2010). Herbal drugs and phytomolecules-based drugs have low solubility, which results in less systemic absorption, which has hampered their development as possible therapeutic candidates. Nanoformulation allows hydrophobic medicines to enter and remain in the tumor region due to the EPR effects (Dutta et al. 2019).

Nanoparticles

Nanotechnology is a multidisciplinary research whose goal is to build more functional atomic, molecular, and supramolecular materials for their effective utilization in health. NPs are divided according to their shapes, sizes, and properties into various classes. NPs have distinctive physical and chemical properties because of their large surface area and nanoscale size. NPs are ideal in catalysis, imaging, medicinal applications, energy-based research, and environmental applications due to these properties they are used not only in domestic but also in commercial applications (Khan et al. 2019b). They are separated into many categories according to their characteristics. Carbon-based nanoparticles, ceramic NPs, metal NPs, lipid-based NPs, semiconductor NPs, and polymeric NPs (Fig. 3) (Aghebati-Maleki et al. 2020). Metallic nanoparticles are widely used in biological sciences for a variety of applications, including drug administration, bioimaging (Gomes et al. 2021), biosensing (Conde et al. 2012a), and catalysis (Tripathi et al. 2019a, b). Ceramic NPs are inorganic non-metallic solids, which are incorporated by heating and successive cooling. Researchers are particularly interested in these NPs as they have possible applications in catalysis (Tripathi et al. 2019a, b), dye photodegradation (Conde et al. 2012b), and imaging (Wang et al. 2021a, b). Semiconductor NPs have properties that are intermediate to metals and non-metals and since they have large bandgaps, they show considerable changes in their properties when the bandgap is tuned (Conde et al. 2012b). As a result, they are key materials in photo optics, photocatalysis, and electronic devices (Saleem et al. 2018).

However, for above all the applications a cost-effective, commercially viable, and environmentally acceptable synthesis approach is required (Gomes et al. 2021). In recent years, Silver Nanoparticles (AgNPs) for having a broad spectrum of biological activities are recommended for new anticancer drug development (Valsalam et al. 2019). NPs were shown to be highly toxic to cancerous cells, so there is a

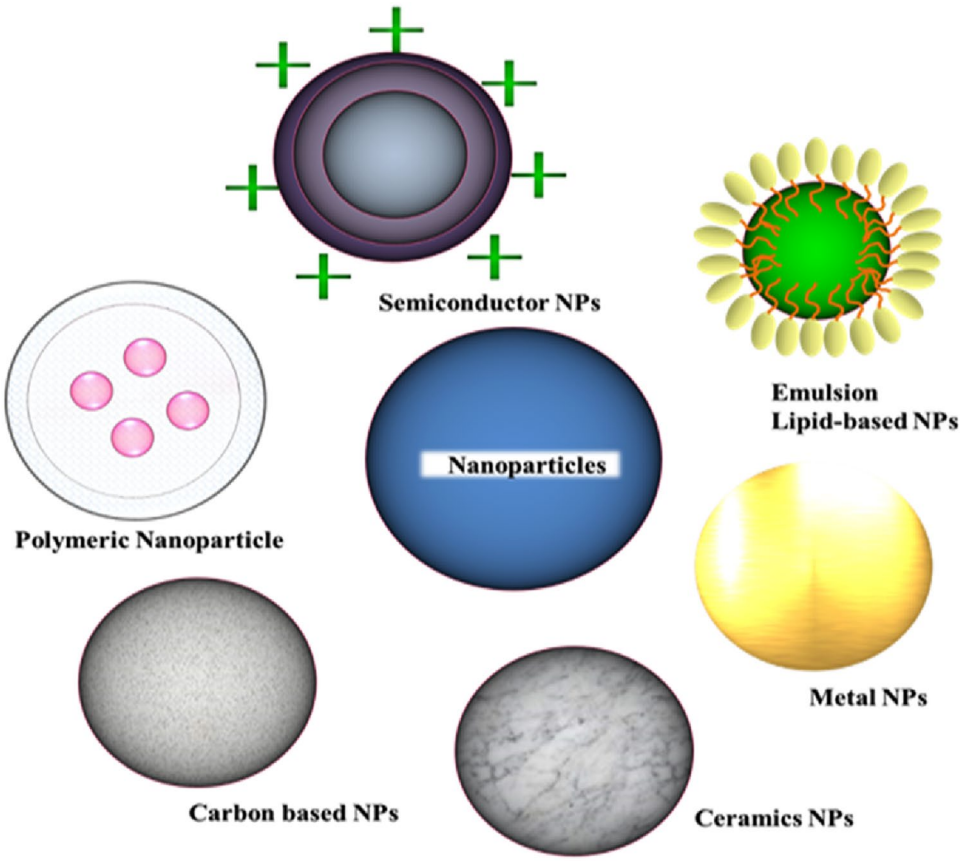

Fig. 3 Different types of nanocarriers

great chance to be used in the diagnosis and therapy of cancer cells (Bhattacharyya et al. 2011). AgNPs reduce tumor cell development, so they can be used as antitumor agents (Gomes et al. 2021), which might be because they could inhibit various signaling cascades which are responsible for cancer development and its pathogenesis. By observing all these it was suggested that AgNPs could be cytotoxic on tumor cells, and also inhibit their development by not affecting non-tumor cells (Priyadarshni and Mahalingam 2017). CeO_2 NPs, like AgNPs, play a potential role in therapeutics due to their unique properties. They show antioxidant and antibacterial properties in a dose-dependent manner. This antioxidant behavior can play a major role in their anticancer preparation. Studies showed that CeO_2 shows no toxicity for aquatic life up to 100 mg/ml and can be a potential candidate for making phyto-nanocarriers (Marghoob et al. 2021).

Role of nanoparticles in cancer treatment

Different processes have been utilized for the prevention of cancer, such as screening, vaccination, surgery, radiation, cryotherapy, and chemotherapy. Chemotherapeutic drug targets cancerous cells exposing healthy cells followed by side effects with the reduction in the immune response and increased vulnerability to host diseases (Peppercorn et al. 2005).

Despite various traditional methods available for the treatment of cancer, a complete cure is still difficult, which has been proven by the fact that in recent years no appreciable reduction was seen in the mortality of cancer patients with more than 50% of deaths (Bray et al. 2018). For these reasons, nanomedicine came into the role intending to find economical components with higher specificity and sensitivity toward cells (Acebes-Fernandez et al. 2020). NPs offer many advantages as they have a significant impact on a variety of cancer cell lines (He et al. 2016a, b), with higher perforation (Bhattacharyya et al. 2011), as well as they can trail NPs inside the body which makes them a better systematic tool with less undesired effects in cancer treatment compared to standard therapeutic procedures (Gomes et al. 2021). The microenvironment in tumor cells and normal healthy cells vary in terms of an acidic environment, a different expression of enzymes and receptors, etc. The main reason for this is difference in pH due to high rate of glycolysis in cancer cells during anaerobic and aerobic conditions. Tumor cells over-express specific receptors compared to normal cells. These specific features affect the function of NPs, so following proper care during nanocarriers design will be an advantage in targeted cancer treatment (Akhtar et al. 2014). Nanoparticles work as drug carrier it changes the pharmacokinetic property of a drug and increases its efficiency with minimum side effects, regulating the drug release process inside the body (Patra et al. 2018), enhancing encapsulation, solubilization, protecting pharmaceutical molecules, as it is smaller in size than the cell, so they can cross-biological barriers and deliver the drug to the specific place, enhances the longevity of drug inside the blood flow, specific target delivery and biocompatibility (Aghebati-Maleki et al. 2020). Some of the most studied NPs for cancer therapeutics are detailed in the following sections.

Carbon-based NPs

Carbon Nanomaterials (CNMs) have piqued the scientific community's interest due to their electronic, optical, thermal, and mechanical properties, as well as their versatile functionalization chemistry and the fact that they appear to be more biocompatible and safer than metal-based nanomaterials for cancer therapeutics. Carbonaceous nanoparticles can load the drug of interest by hydrophobic interactions or $\pi - \pi$ stacking and can be employed as effective drug delivery platforms because of their inherent hydrophobic character. Carbon nanomaterials, such as graphene, fullerenes, Carbon Nanotubes (CNTs), and Carbon Quantum Dots (CQTs) are the most commonly employed for cancer treatment (Saleem et al. 2018). These exhibit various properties of commercial interests, like high strength, electrical conductivity, electron affinity, structure, and versatility (Astefanei et al. 2015). CNMs possess various sizes in Acidic tumor Microenvironment (TME); they can penetrate deep into tumors, which is aided by the EPR effect. Furthermore, CNMs are biodegradable, bolstering their potential as cancer treatment agents in the future. Cancer stem cells, tumor migration and invasion, tumor-associated inflammation, hypoxia, metabolism, and angiogenesis are among the pathways that CNMs can regulate (Cheng et al. 2021); thus, they are attractive nanocarriers and nanomedicines for TME-targeted cancer treatment due to their physiochemical features (Saleem et al. 2018).

Metal NPs

These are purely made from metal precursors having the characteristic of Localized Surface Plasmon Resonance (LSPR) and distinctive optoelectrical properties. These are used in cutting-edge materials because of their precise and shape-controlled synthesis (Dreaden et al. 2012). Nobel metal NPs have distinctive qualities, such as high surface-to-volume ratio, wide optical properties, simplicity of production, simple surface chemistry, and functionalization, which make them promising candidates for cancer therapies in clinics (Table 2) (Conde et al. 2012a). Metal NPs use two ways to target tumor cells: passive targeting and active targeting. The EPR effect is a passive phenomenon in which NPs of specific sizes aggregate in tumor tissue at a greater rate than in normal tissues, and due to their leaky vasculature,

arrangement, and inadequate lymphatic drainage, tumor tissues are more permeable to macromolecules than healthy tissues, allowing nanoparticles to rapidly infiltrate into malignant cells and destroy them. As NPs have distinctive shapes and enhanced vascular permeability, metal NPs can be used to target cancer cells (Table 2). When compared to passive targeting, active targeting has greater specificity and selectivity toward cancerous cells while causing minimal or no harm to healthy cells. The use of functionalized nanoparticles to deliver chemotherapeutic agents not only improves therapeutic efficacy but also helps prevent drug resistance (Sharma et al. 2018a).

Polymeric NPs

Polymeric NPs are normally organic-based NPs and mostly their shape is nanosphere or nanocapsules (Mansha et al. 2017). Curcumin-loaded polymeric nanoparticles, PLGA,

Table 2 Plants studied for the synthesis of nanoparticles (NPs) in cancer therapeutics

Plant's name	Part utilized	Nanoparticles	Cancer cell line	References
Abelmoschus esculentus	Pulp	AgNPs, AuNPs	Lymphoma cancer	Korani et al. (2021)
Abutilon indicum	Leaf	AgNPs, CuO NPs	COLO205 cells, A549, MDA-MB-231	Sathiyavimal et al. (2022)
Achillea biebersteinii	Flowers	AgNPs, AuNPs	MCF-7 cells, NTERA-2	Baharara et al. (2015) and Mobaraki et al. (2021)
Acorus calamus	Rhizomes	ZnONPs	SK-MEL-3 cells	Vakayil et al. (2021)
Allium sativum	Whole plant	AuNPs	HT-29, HCT116	Liu et al. (2021)
Alternanthera sessilis	Airy potion	AgNPs, AuNPs	MCF-7 cells	Firdhouse and Lalitha (2015, 2020)
Andrographis echioides	Leaf	Solid lipid NPs, PLGA NPs, AgNPs	MCF-7 cells, HepG2, HeLa cells	Elangovan et al. (2015) and Parveen et al. (2019)
Artemisia marschalliana	Airy Portion	AgNPS, AuNPs, ZnNPs, CuNPs	AGS cells, HCT-116, HT29	Andleeb et al. (2021)
Artemisia princeps	Leaves	AgNPs	A549 cells	Gurunathan et al. (2015)
Azadirachta indica	Leaves	AuNPs, ZnONPs	SiHa, HeLa, Hek-293 cells	Agarwal et al. (2018)
Butea monosperma	Leaves	Fe_3O_4	A549 and B16F10 cells	Behera et al. (2020)
Calotropis gigantea	Latex	ZnONPs	MCF-7, HeLa, HEK-293	Gobinath et al. (2022)
Curcuma longa	Rhizome	Bipolymer NPs	Hep3B, hBMSCs	Montalban et al. (2018)
Alstonia scholaris	Bark	Glycol-chitosan NPs, PLGA NPs	HeLa, Vero cells	Tripathi et al. (2019a, b) and Zheng et al. (2019)
Terminalia arjuna	Fruit	MnO_2	MCF-7	Reddy et al. (2022)
Ziziphus mauritiana	Fruit	Ag/AgClNPs	MCF-7	Kabir et al. (2020)
Manilkara zapota	Leaf	AgNPs	MCF-7	Madakka et al. (2021)
Ficus benghalensis	Dry powder	CuNPs	Oral cancer	Imtiaz et al. (2022)
Betula pubescens	Whole plant	PLGANPs, lipid NPs	HCC, MCF	Kim et al. (2021)
Withania somnifera	Root	TiO_2 NPs	$HepG_2$, HEK-293	Al-Shabib et al. (2020)
Glycyrrhiza glabra	Root	SeNPs	PC12	Maheswari et al. (2020)
Cymodocea serrulata	Whole plant, leaves	AgNPs	HeLa, A549 cells	Chanthini et al. (2015) and Palaniappan et al. (2015)
Dimocarpus longan	Peel	AgNPs	H1299, BxPc3, VCaP cells	He et al. (2016a, b)
Erythrina indica	Root	AgNPs	Hep-G2 cells	Sre et al. (2015)
Excoecaria agallocha L	Leaf	AgNPs, AgONPs	B16F10 cells	Banerjee et al. (2017)
Gymnema sylvestre	Leaf	AgNPs	HT29 cells	Arunachalam et al. (2015)
Moringa olifera	leaf	AgNPs, AuNPs, Ag/AuNPs	HepG2, MDA-MB-231, MCF-7	Gupta et al. (2020)
Piper longum	Fruit	AgNPs	MCF-7 cells	Krishanan et al. (2016)
Syzygium cumini	Flower	AgNPs	MCF-7, HeLaandHek-293 cells	Mittal et al. (2016) and Ramar et al. (2015)
Tabernaemontana divaricata	Leaves	AgNPs	MCF-7 cells	Devaraj et al. (2014)
Taxus yunnanensis	Callus	AgNPs	SMMC-7721 cells	Xia et al. (2016)
Vitex negundo	Leaf	AgNPs, ZnONPs	HCT15 cells	Agarwal et al. (2018)

a biodegradable, biocompatible synthetic polymer of 100–200 nm in size, are broadly studied in cell culture and animal models (Yallapu et al. 2013). Advantages of using polymeric nanoparticles in therapies include refined physiochemical properties, the ability to easily play with several types of molecules, biodegradable, non-toxic, overcome limitations, like poor solubility, and can be used as an alternative therapeutic agent (Indoria et al. 2020). Poly(lactic-co-glycolic acid) and poly(lactic acid) are synthetic polymers that have been approved by the FDA for human use. Multifunctional NPs can facilitate visualization of malignant cells, target them, and destroy cancer cells without damaging healthy cells in the process (Ahlawat et al.2018).

Lipid-based NPs

These NPs have lipid moieties and can be used in a variety of biomedical applications. A lipid NP is typically spherical, with a diameter ranging from 10 to 1000 nm. Lipid nanotechnology (Mashaghi et al. 2013) is a specialized topic that focuses on the design and synthesis of lipid NPs, which can be utilized for a variety of applications, such as medication administration and RNA release in cancer therapy. Liposomes, Solid Lipid Nanoparticles (SLNs), and Nanostructured Lipid Carriers (NLCs) are Lipid-Based Nanoparticles (LBNPs) that generate a lot of attention in drug development and cancer treatment (Wang et al. 2021a, b). These NPs can transport both hydrophobic and hydrophilic molecules, have very low or no toxicity, and extend the duration of pharmacological activity by having a longer half-life and regulated drug release. Chemical changes to lipid nanosystems can be used to evade immune system detection or to improve medication solubility. They can also be made in pH-sensitive formulations to increase drug release in an acidic environment, and they can be linked to antibodies that target tumor cells or their receptors (such as folic acid); because of their biocompatibility and adaptability, liposomes are the most extensively utilized LBNPs (Garcia-Pinel et al. 2019), with the help of their lipophilic tails, amphiphilic phospholipids self-assemble into a spherical lipid bilayer structure, providing a framework for the encapsulation of hydrophobic medicines (Mashaghi et al. 2013). As opposed to this, the hydrophilic heads of phospholipids form an aqueous core and external surface that can contain hydrophilic chemicals. Both charge–charge interactions and interactions with chemical linkers on the liposomal surface can result in the encapsulation of different medicinal compounds into liposomes. It is significant to note that the encapsulation of therapeutics within various liposomal compartments enables safe and precise drug delivery because liposomes can shield enclosed cargos from immune system degradation while transporting them across biological membranes where the free drugs are frequently incompatible (Wang et al. 2021a); however, SLNs and NLCs have recently gained a lot of attention (Garcia-Pinel et al. 2019).

Phyto-nanocarriers and their role in cancer therapy

Nanoparticles synthesized through the conventional methods cause toxicity therefore using green synthesis, i.e., reduction by application of antioxidant plant material results in not only less toxicity (Chanthini et al. 2015) but also more stability. The manufacture of nanoparticles using plant extracts is a straightforward one-step reduction technique with large-scale production (Table 2) (Agarwal et al. 2018). Plant-based methods may also help in achieving desired NPs size (Banerjee et al. 2017; Agarwal et al. 2018) as well as also offer eco-friendliness, economic effectiveness (Baharara et al. 2015), and compatibility for pharmaceutical and biomedical applications (Baharara et al. 2015; Arunachalam et al. 2015). Plant extracts/ molecules act as both capping and stabilizing agents for nanoparticle synthesis (Banerjee et al. 2017) (Fig. 4). Phytomolecule and nanoparticles can help achieve this goal by passively accommodating many solid tumors due to the Enhanced Permeability and Retention (EPR) effect. This effect is due to the abnormalities in tumor vasculature as well as the poorly developed lymphatic system. This limits the drainage of tumor tissue molecules, following the discovery of the EPR effect. In visualizing anticancer new products, which are available commercially, were obtained from natural sources either by structural natural compounds modification or by new compounds synthesis (Table 2). Phytonaocarriers has enhanced effect due to their biocompatibility (Yadav and Sangwan 2022), less cytotoxicity, less resistance, and dynamic physiochemical properties used to treat different cancers (Dhupal and Chowdhary 2020). These well-known plant extracts and phytochemicals (the plant secondary metabolites) with promising anticancer properties have been encapsulated in biocompatible and biodegradable polymeric nanoparticles (Dutta et al. 2019; Indoria et al. 2020), solid lipid nanocarriers (Garcia-Pinel et al. 2019), carbon-based NPs (Saleem et al. 2018), nanocapsules, liposomes, metallic nanoparticles (Valsalam et al. 2019), and non-metallic NPs (Dhupal and Chowdhary 2020). Green synthesized metallic nanoparticles using *Achillea biebersteinii* plant flower extract showed a significant anti-apoptosis against human breast cancer cell line (MCF-7) (Baharara et al. 2015); NPs synthesized using *Excoecaria agallocha* L., leaf extracts showed potential anticancer properties against several cell lines, such as Murine Lung Adenocarcinoma (3LL), Murine Ehrlich Ascites Carcinoma (EAC), Murine Colon Cancer (CT26), and Murine Melanoma (B16F10) cells with no side effects. In the case of B16F10 cells, cell death was caused by nuclear translocation

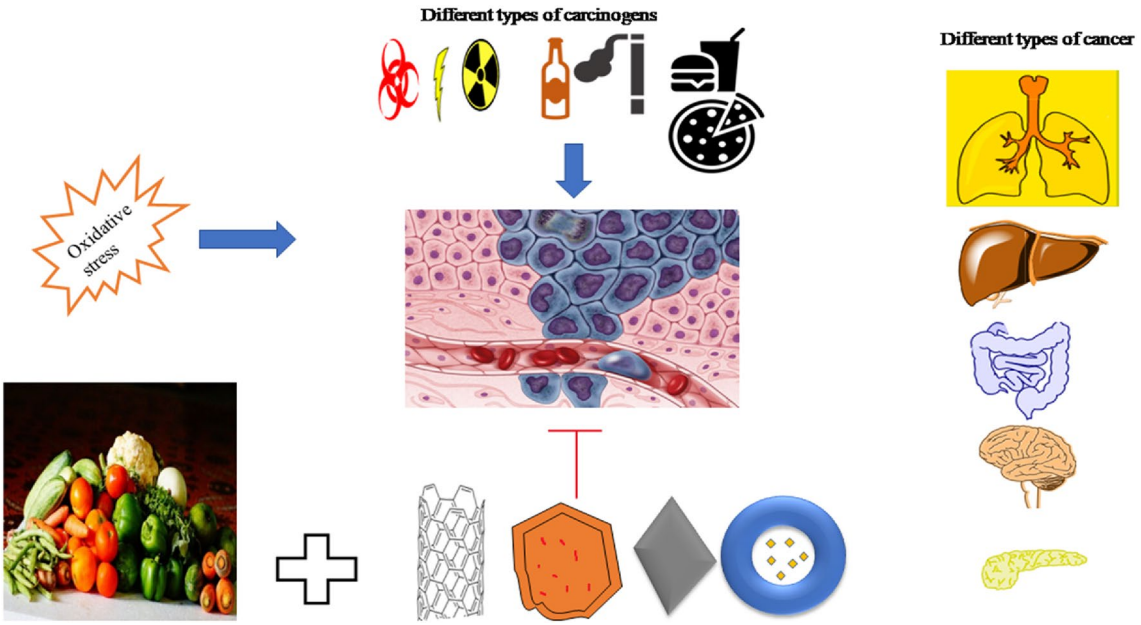

Fig. 4 Schematic presentation of phyto-nanocarriers used as anticancer

which was observed with the help of fluorescence microscopy and flow cytometry (Benerjee et al. 2017). Cytotoxicity studies of NPs synthesized using *Nelumbo nucifera* and *Cymodocea serrulata* found that these plant extracts have a significant role in inhibiting lung cancer (HeLa cells) (Chanthini et al. 2015). Gold NPs synthesized using *Antigonon leptopus* powdered extract and copper oxide NPs synthesized using *Acalypha indica* have cytotoxic properties against MCF-7 breast cancer cell lines (Greenwell and Rahman 2015). When berberine was encapsulated in chitosan NPs, its bioavailability was improved without changing its structure or performance. By specifically targeting cancer cells, it also improved cytotoxic behavior against them. Oral administration increased bioavailability according to in vivo tests, while berberine capsules were allowed for up to three times lower doses (Chou et al. 2013). Camptothecin is a strong anticancer compound, but its unstable lactone ring and limited solubility made it unsuitable for clinical use. More than 80% of the hydrophobically modified glycol chitosan nanoparticle could be loaded with it. It aids in defending the lactone ring from physiological circumstances. It was also shown to have excellent antitumoral efficacy and to penetrate tumors more deeply, likewise when curcumin was encapsulated with PLGA, it showed enhancement in biological activity against prostate cancer (Dhupal and Chowdhury 2020).

Conclusion

The widespread occurrence of cancer worldwide is a matter of great concern. The existing therapies available, such as radiation, chemotherapy, and other medications are widely used but they have adverse effects associated with them; this review mainly highlights various alternative methods that have been explored and might have minimal or negligible side effects. Various metabolites present in fruits and vegetables are effective in the prevention or inhibition of cancer. Studies have revealed that plant-based molecules possess potent anticancerous properties. The drug formulations of these molecules are restricted due to their limited occurrence, aqueous solubility, and bioavailability. Nanotechnology has arisen as a modern way of therapeutics to overcome some of these issues and treat various stages of cancer by targeted drug delivery of anticancerous agents. Nanoparticles synthesized using plant parts have shown to be effective in in vitro cell lines. Several specific metabolites, such as resveratrol, acacetin, curcumin, epigallocatechin, and gallate, act as a potent scavenger of free radicals and hence protect from oxidative stress. These molecules serve to exhibit properties to be used as phyto-nanocarriers. A few studies have been reported for the toxicity and allergic reactions in people treated with nanodrugs with varying compositions. Therefore, an extensive study is further required to validate the observations for exposure as well as the level of chemical composition used for the study. The dose, shape, surface chemistry, purity, and exposure route also need to be further warranted.

Acknowledgements NY is thankful to UGC (536 CSIR-UGC NET DEC. 2018) for fellowship. NSS is thankful to DST for financial grant. The funding agency had no role in the interpretation or writing the manuscript.

Declarations

Conflict of interest The authors state that there are no conflicts of interest to disclose.

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