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Phytochemical-based nanodrug delivery in cancer therapy

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Abstract--There are estimated to be 13.1 million cancer deaths by 2030, with 7.6 million deaths occurring each year. Phytochemicals have long been used in traditional medicine to cure cancer. However, conventional therapy for metastatic illness may fail if cancer cells become resistant to multiple anticancer drugs. Phytochemicals encapsulated in nano-based medication delivery devices were studied for their cancer- and chemo-preventive properties. Nanocarriers containing phytoconstituents have been studied in terms of loading efficiency, nanocarrier size, the release profile of the drug, and cell inhibition and treatment tests.

Keywords---nanocarrier, cancer, phytochemicals, cancer prevention.

Introduction

There are an estimated 7.6 million deaths from cancer in the United States each year, and that number is anticipated to climb to 13.1 million by 2030. If precancerous cells can be detected early and treated, individuals of any age or stage of life should expect to live longer. The breast, uterus, lungs, pancreas, and skin are all at risk for cancer. With its capacity to inhibit tumor growth and target several metabolic pathways seen in cancer cells, the term "natural substance" should be utilized. Phytochemicals are found in vegetables, fruits, and spices because they are naturally occurring bioactive substances. Phytochemicals are found in many traditional remedies to maintain and prevent health and sickness and cancer (Afifi-Yazar, Kasabri, & Abu-Dahab, 2011; Agyare et al., 2018). Phytochemicals have been the subject of much investigation as a cancer treatment in several countries during the last few decades (Mathur & Vyas, 2013; Muchakayala et al., 2022). However, it will be some time before phytochemicals are commonly used in cancer therapy, despite their promise. Several common problems include solubility, cell penetration limitation, liver disposition, and quick absorption by normal tissues. The widespread dissemination of phytochemicals brought on an accumulation of drugs in normal organs. Phytochemical-targeted treatments' rapid clearance and short half-life are also hazardous. The Food and Drug Administration estimates that 25 and 48 percent of currently approved medications are derived from plants (FDA) (Ahmadi et al., 2020; Akhtar, Saleem, Alamgeer, & Saleem, 2019) (Figure 1).

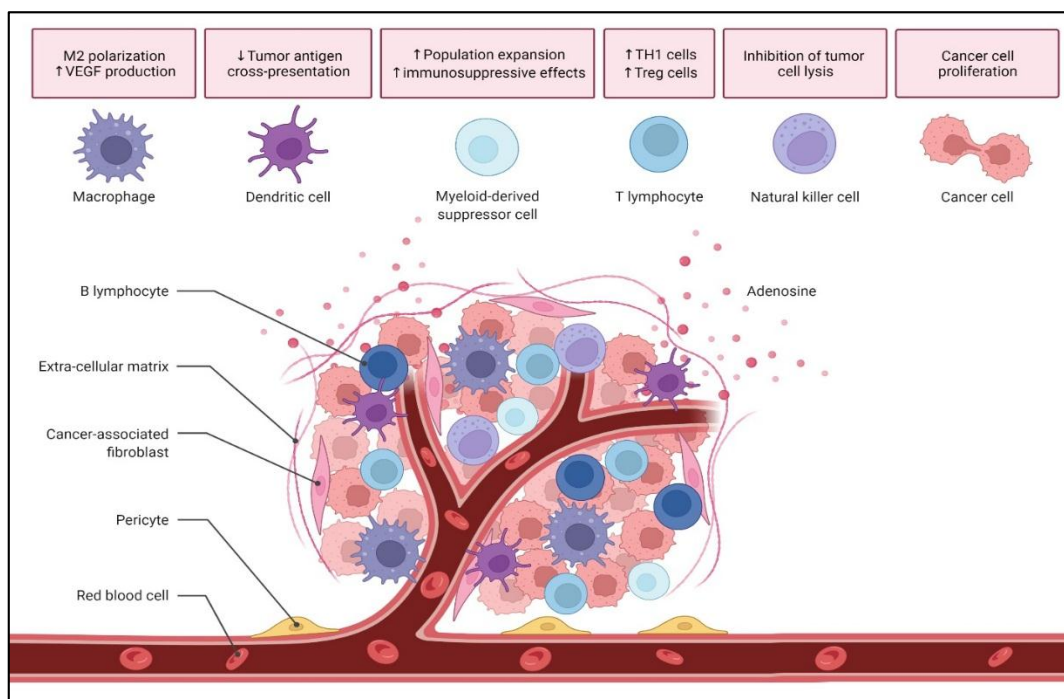


Figure 1: Effects of Adenosine from the tumor environment

Anti-inflammatory and anticancer properties set these compounds apart. Phytochemical-derived chemicals may be abundant in green leafy vegetables and

other plant foods. More than 10,000 phytochemicals have been used in cancer treatment because of their anticancer properties. An anticancer medication may benefit from phytochemicals, which may reduce adverse effects. However, there is also the issue of medication resistance, which may emerge for several reasons, preventing phytochemicals from being employed in cancer therapy (Akkol, Dereli, Sobarzo-Sánchez, & Khan, 2020; Alami Merrouni & Elachouri, 2021). Phytochemicals face yet another obstacle with the advent of multidrug resistance (MDR). Conventional chemotherapy is often considered the best option for individuals with metastatic cancer. Failure to recognize cancer cells may lead to the development of resistance to a broad spectrum of anticancer drugs. Nanotechnology has great potential for bringing improved cures, gadgets, and diagnostics to market quicker and cheaply when used in pharmaceutical formulations and medical treatments (Subramanian et al., 2022; Valluri et al., 2021). The limitations of phytochemistry and the health issues may be solved by nanomedicines that increase solubility, bioavailability, and cell absorption. Since these nanomedicines are designed to serve several functions, they have very minimal contact with the circulation and may maintain therapeutic concentrations for extended periods. Nanomedicines' tumor-targeting qualities are mainly owing to their improved permeability and retention capabilities (IPR) (Almatroodi, Almatroudi, Alsahli, Khan, & Rahmani, 2020; Alonso-Castro et al., 2011). Blood vessels and lymphatic drainage systems are often misaligned in solid tumors. Because of the IPR phenomenon, nanomedicines and macromolecules may "leak" from blood vessels surrounding tumors (Asemani, Zamani, Bayat, & Amirghofran, 2019; Aune, 2019).

Tumors that do not have enough lymphatic drainage, on the other hand, may develop cancer cell clusters. The EPR effect does not exist in normal tissues. Biocompatibility and the size of nanomedicines are critical to the EPR effect. The molecular weight of macromolecules and nanoparticles must be at least 40 kDa to induce the EPR effect. For the EPR effect to work, the drug must be in circulation for an extended period. Low molecular weight phytochemicals are responsible for the vast majority of clearance and distribution in healthy tissues and organs of phytochemicals (Balachandran & Govindarajan, 2005; Benarba & Pandiella, 2018).

Additionally, MDR is a significant factor in preventing phytochemical therapy for cancer patients. To overcome the MDR effect, phytochemicals may be transported via nanocarriers. In addition, drug resistance may be reduced by modifying biophysical interactions between nanomedicines and the lipids on cancer cell membranes.

Phytochemicals' Molecular Mechanisms and Targets

The antibacterial and antiviral properties of phytochemicals found in foods, their antimicrobial and nitration-suppressing properties, and their ability to inhibit DNA binding are well-established. It has also been studied in detail the metabolism of steroid hormones and estrogen (Bhatnagar, Thomas, & Kim, 2013; Blažejová & Hošek, 2019).

Antioxidant

Aerobic respiration's energy and low-concentration chemicals are essential for subcellular functions like signal transmission, enzyme activity, and gene expression. Cellularly. There are ozone, hydrogen peroxide, and singlet oxygen reactants. Oxidative stress arises when a pro-oxidant equilibrium is interrupted. Because of this, lipids and proteins may be damaged, and DNA can be altered by reactive oxygen species (ROS)(Vyas, Mathur, Patel, & Patel, 2017). Phytochemical antioxidants may have paradoxical effects depending on cell type and concentration. Decreases ROS levels and reduces oxidative stress before cancer cell development is halted (Bouhaous, Miara, Bendif, & Souilah, 2022; Buyel, 2018). Emodin's antioxidant qualities cause free radicals to be reduced and removed. An early stage in the radical scavenger enzyme reaction might be activating emodin, an electron transfer, or allylic hydrogen abstraction enzyme. In interaction with cellular oxygen, it produces a superoxide anion. Proteins and nucleic acids may be damaged by ROS produced by cancer cells (Caamal-Fuentes, Torres-Tapia, Simá-Polanco, Peraza-Sánchez, & Moo-Puc, 2011; Calderón-Montaño, Burgos-Morón, Pérez-Guerrero, & López-Lázaro, 2011).

Tumor Induction and Oncogene Expression Inhibition Suppress Gene Expression

Oncogene and tumor suppressor genes have a role in the genesis of cancerous cells. Overexpression of an oncogene may lead to malignant cells even though oncogenes are involved in various cell activities and mitosis. Several signaling pathways prevent malignant cells from growing when tumor suppressor genes, which are underexpressed in cancer cells, are suppressed. A cancer-promoting protein called Bcl-2 shields cancer cells from free radical damage. In contrast, the anticancer gene Bax causes cancer cells to die. When administered to myeloid, programmed cell death-proficient HL60 cells, or programmed cell death-resistant K562 cells, the medication Noscipine boosted Bax expression. Lymphocytic leukemia chronic cells had high levels of Bax but low levels of apoptosis and Bcl-2 (Cragg & Newman, 2005; Dai et al., 2016).

The Cell Cycle arrest

Cell cycles G1, G2, S, and M are all sorts of cycles. These checkpoints ensure the appropriate replication and division of DNA. The cell cycle may continue or halt at a checkpoint, allowing for DNA repair if damage occurs. G1:S or G2/M checkpoint (cells assess the efficacy of their DNA, the presence of specific growth factors, and cell size) is often successful in halting the development of cancerous cells (if mitosis conditions, such as cell size, DNA quality, and nutrients, are met). At the G2:M checkpoint of the cell cycle, Luteolin suppresses the growth of human stomach and prostate cancer cells and melanoma cells in animals (Dang & Van Damme, 2015).

Apoptosis

Cell death that is "planned" or "physiological" must take place to preserve the tissue's integrity. Unlike other organisms, the cell can devour its genetic material.

Apoptosis-inducing anticancer medicines have long been sought since they are so crucial in the battle against cancer. The death receptor (extrinsic) and intrinsic mitochondrial processes of cell apoptosis are two of the ways cells die. Berberine induces apoptosis both internally and externally (Dávalos et al., 2021). When Berberine is used as an apoptosis-inducing medication in the malignant SCC-4 squamous tongue cell of the tongue, it increases cell growth. In addition, it activates p53 and generates ROS in SW620 human colonic cancer cells to drive the intrinsic apoptotic pathway (Desai et al., 2008).

Control of the Signaling Pathway

In healthy cells, resistance is given via a signaling system that is intricately coupled and partly layered. Intracellular and intercellular signaling anomalies enable malignant cells to flourish and grow unchecked. Cancer medicines that currently block or regulate signal transmission are being tested in clinical studies. Thymoquinone may modify AKT/PKB signaling pathways in malignancies such as multiple myeloma, squamous cell carcinoma, and prostate cell lines (Devadasan, Raman, & Dasararaju, 2021).

Inhibition of invasion and metastasis via reducing cell-to-cell adhesion (AIM)

Metalloproteinases matrix (MMPs), which are overexpressed in diseased tissues, help spread cancer cells. MMPs and MMP inhibitors are now being tested in phase I clinical trials to see whether they affect cancer cell invasion. For example, SCC-4 and A459 lung cancer cells have been affected by silibinin's ability to change the expression of MMP-2 (El Omari et al., 2021).

To activate or inhibit enzymes

Phase I enzymes, which prevent carcinogenesis, may be activated or inhibited by phytochemicals (overexpressed in malignant tumors). For example, COX-2 levels were lowered in macrophages from mice and breast cancer cells treated with Apigenin and Nobiletin (phase II enzyme) (El-Harakeh, Al-Ghadban, & Safi, 2021).

Anti-Angiogenesis

Developing new blood vessels from preexisting ones is a critical biological mechanism that supports cancer growth and metastasis. Tumors generate VEGF, FGF, and other proangiogenic chemicals. Tyrosine kinase inhibitors have recently been employed to block VEGF and VEGFR2 using antibodies. According to a recent study, the natural plant compound ursolic acid may inhibit B16F-10 cancer cells (Epifano, Curini, Marcotullio, & Genovese, 2011).

Anticancer properties of phytochemicals Rottlerin

The *Mallotus philippinensis* tree (*Mallotus Kamala*), which is endemic to the Philippines, produces the natural polyphenol rottlerin. Rottlerin, an apoptosis-

competent cytotoxic drug-resistant to apoptosis, kills cancer cells and tumors. However, its cancer-fighting qualities remain a mystery (Garima et al., 2020).

Pathways involved in cell death

Some examples include the DR4/DR5 TRAIL receptors being stimulated by intravenous Rottlerin injection, and caspase-8 is activated. In addition, the mitochondrial Bcl-2 family may be able to release cytochrome C. Inhibition of the PI3K/Akt/mTOR pathway and activation of the caspase cascade may be necessary to initiate rottlerin-induced apoptosis. Rottlerin affects DNA repair because it affects H2AX, a DNA damage response marker, which influences apoptosis. Caspase-dependent cell death occurs when the stress-responsive JNK pathway is engaged, which results in H2AX activation (George, Dellaire, & Rupasinghe, 2017).

Inhibitors of Nuclear Factor kB

Transcription factors are implicated in a wide range of cancers. For example, the IKK-NF- κ B signaling pathway is essential for minimizing host damage and establishing treatment resistance during cancer therapy. "one's own set of genetic material. In MCF-7 cells, Rottlerin improves rsTRAIL sensitivity by decreasing NF- κ B transcription and speeding up the processing of the executioner caspase (Gezici & Şekeroglu, 2019). Although, on the other hand, in HT-29 and MCF-7 cancer cell lines, Rottlerin promotes activity while blocking the TNF-dependent pathway. NF- κ B may be inhibited in several ways in different cell types (Greenwald, 1996) (Graham, Quinn, Fabricant, & Farnsworth, 2000).

Berbamine

Its natural component has anti-tumor actions on a broad spectrum of cancer cell types and derivatives. The chemical, despite its function, is not as damaging to normal human cells. However, BBM induces apoptosis in the estrogen-positive human regular mammary epithelial cell line, MCF10A, but not in the MDA-MB-231 or MCF-7 human breast cancer cell lines. BBM causes apoptosis, or the death of cells, in a wide variety of cancerous cells and tumors. Reduces Bcl-2 and Bax protein levels, enhances P53 and Fas expression, modifies the mitochondrial membranes, and suppresses BCR-ABL gene and P210 expression levels. All of them are feasible options for BBM-induced apoptosis (Gul, Singh, & Jabeen, 2016).

By lowering the Bcl-2:Bax protein ratio in A549 cells, BBM increases the pro-apoptotic Bax and decreases the anti-apoptotic Bcl-2. Apoptosis is induced when activated by the JNK-c-Jun/AP-1 signaling pathway, resulting in reactive oxygen species (ROS) generation. Another BBM derivative, bbd24, reduced liver cancer cells and accelerated cell death in mice by blocking calmodulin/Ca²⁺-dependent protein kinase II (CAMKII). There may be a reduction in the anti-apoptotic protein Bcl-2 and an increase in pro-apoptotic protein Bcl-xL when BBM and gemcitabine are combined (Bax, Bid) (Hartwell, 1969).

Sparstolonin B

Scientists in *Sparganium stolonifera* have not yet found an entirely novel bioactive molecule. SsnB inhibits cell growth, halts cell cycle progression, and induces apoptosis in a range of neuroblastoma cell lines. ROS generation by neuroblastoma cells with genetically heterogeneous origins may cause the apoptotic effect. SsnB prevents oxygenation-induced inflammation and reduces the manufacture of several inflammatory cytokines by inhibiting cancer cell blood supply (Hartwell, 1971). Anti-angiogenic SsnB reduces the expression of mRNA encoding proteins that control the cell cycle. According to recent results, a potent antagonist of TLR2 and TLR4 has inhibited the ERK1/2 and JNK pathways. Inflammation brought on by hypoxia and oxygenation is decreased as a consequence (Hasanpourghadi et al., 2017).

Sulforaphane

You'll find it naturally in veggies like cabbage and broccoli. When SFN inhibits the protein kinases necessary for cell proliferation and expansion, it stops the cell cycle in its tracks and causes cell death. SFN induces ROS generation in cancer cell lines, resulting in cell death, DNA damage, and aberrant mitosis. Mitochondrial dysfunction and apoptosis may be caused by SFN, whereas pro-survival pathways such as nuclear factor kappa B are suppressed. SFN activated caspases 3, 8, and 9 to inhibit the Cdc2/Cyclin B1 complex without causing p53 activation of caspases 3, 8, and 9. Increasing the expression of p21(CIP1/WAF1) this also inactivated PARP (Hazafa, Rehman, Jahan, & Jabeen, 2020). HDAC6 enzyme inhibitors increase the acetylation of p21 and Bax promoters to prevent caspase-mediated cell death. SFN inhibits HDAC6 activity, increasing the acetylation of chaperone HSP90 in prostate cancer. Most cell lines investigated show that SFN inhibits the mTOR and AKT survival pathways. The transcriptome was altered due to SFN's inhibition of Cdk1-encoding transcription through courses such as Cdc25C regulation (Henderson, Ross, & Pike, 1991).

Plumbagin

Plumbagozeylanica L, *Juglansregia*, *Juglansnigra*, and *Juglanscinerea* roots contain naphthoquinone. To suppress the mTOR/PI3K/Akt pathway, PLB reduces its phosphorylation of this pathway. The anti-apoptotic AKT protein is the fundamental building component of PLB. In tongue squamous cell carcinoma cells, PLB suppression of the PI3K/Akt/mTOR and p38 MAPK signaling pathways induce proliferation and autophagy (Hilker & Meiners, 2011). It is possible to employ PLB as an indicator of cell development and death because of its capacity to decrease cyclin D1 gene expression. Oncogenic cell growth and development depend heavily on the NF- κ B transcription factor. In previous studies, cancers such as lymphoid and myeloid malignancies have been demonstrated to have active NF- κ B. NF κ B and IB kinase-NF κ B signaling pathways are critical in cancer treatment because they promote resistance and minimize host harm. When PI3K and Bcl-2 are inhibited, glioblastoma cells become more susceptible to apoptosis. After treatment with PLB, NF- κ B, casp-7, Bad p53, and Bcl-2 were elevated in MCF-7 cells. PLB has a significant pro-autophagic effect on cells trapped in the G2/M phase while increasing intracellular ROS levels in cell lines taken from

human lung cancer patients (H23 cells and A549) (Hussain et al., 2018). In human lung cancer cell lines, PLB suppresses NF- κ B/p65 nucleus translocation, enhances caspase-3-9 activity, lowers Bcl-2 expression, and regulates Bak, Bax, and Cytochrome C expression. The reduction in PC-3M cell growth and metastasis caused by PLB inhibits the angiogenesis markers CD31 and VEGF.

Shogaol

Someday, people living with cancer may benefit from using ginger's key medicinal ingredient, Six-Shogaol (*ZingiberOfficinale*). 6-shogaol's ability to induce caspase-mediated cell death in many malignant cells has been widely recognized as an effective anticancer therapy. When 6-shogaol is added to a person's diet, many genes are suppressed. Gemcitabine treatment becomes less effective against pancreatic cancer cells when NF- κ B and cell survival regulators are inhibited. Activation of the p53 pathway may lead to the production of proliferative chemicals linked to mitochondria and intracellular glutathione levels. Cell death may occur if the Akt signaling pathway is disrupted and cyclin D1/3 synthesis is reduced (Khalid, Ayman, Rahman, Abdelkarim, & Najda, 2016).

Camptothecin

Many plants, including *Canzptothecaacirminata* and *Mappiafoetida*, contain the alkaloid camptothecin. Topoisomerase I, an enzyme that aids in unwinding DNA supercoils, is targeted by this potent anticancer phytochemicals. Camptothecin derivatives are presently being tested in clinical trials. Camptothecin and twenty-(S)-9-nitrocamptothecin were tested in phase I clinical studies on 52 and 29 patients with resistant malignancies. With both medications, some people with breast cancer, prostate cancer, and melanoma had anticancer effects (regression of skin tumor nodules) (A. Khan et al., 2021). In addition, there were partial responses in patients with ovarian cancer (reduction in extensive liver metastases) and breast cancer (disappearance of cutaneous metastases). Other studies have demonstrated that 9-nitrocamptothecin aerosolized from liposomal carriers help treat individuals with advanced lung cancer (stabilization and partial remissions) (T. Khan et al., 2019).

Phytoceutical Extraction from Plants

Apigenin

Celery, parsley, and chamomile tea contain significant amounts of yellow flavonoid 4,5,7,-trihydroxyflavone. Apigenin's antioxidant characteristics, notably its ability to scavenge free radicals, has been related to many of its biological effects in vitro and in vivo in numerous mammalian systems. Apigenin has been discovered to kill cancer cells from the breast, prostate, and lung. Class II categorization for 82–84 APG was made because of its low solubility and high permeability. A375 skin cancer cell proliferation may be inhibited by PLGA nanoparticles that contain the antioxidant Apigenin, researchers believe (Klein-Júnior et al., 2020). The researchers developed spherical NPs with an 87 percent entrapment efficiency and an average diameter of 101.3 0.004 nm. By protecting the drug and enhancing its photostability, the APG-PLGA nanoparticles

outperformed the competition in the sun. First, the drug was put on the market for 16 hours, then three days of controlled release. APG-NPs (IC₅₀ = 15 M) was more effective than pure APG (IC₅₀ = 25 M) when suppressing cell proliferation. Apoptosis is characterized by cell shrinkage and membrane blebbing, two frequent morphological changes. The fact that NPs were found in the brain tissue of mice suggests that they can cross the blood-brain barrier. It was previously shown that PLGA nanoparticles containing Apigenin, an anti-carcinogenic compound, significantly delayed UVB–Benzo[a]pyrene-induced skin cancer in mice (Kooti et al., 2017).

Solution HS 15 and Pluronic P123 were used to create polymeric micelles containing Apigenin, according to Zhai et al. Thin-film dispersion of polymeric micelles led to an entrapment efficiency of 96%. Polymeric micelles released Apigenin for 36 hours, confirming their long-term effectiveness as drug delivery vehicles. Polymeric micelles containing Apigenin were more effective than the pure drug in controlling HepG2 and MCF-7 malignant tumors because they enhanced solubility and greater cell absorption (Kostecka, Pienta, & Amend, 2021).

Dihydroartemisinin and Artemisinin

As part of their research, Neda and her colleagues developed artemisinin-enriched reverse-phase liposomes using this approach. Artemisinin-PEGylated Liposomes were also examined. Nanoformulation diameters of 500 nm and 455 nm contained 96% and 92 percent of artemisinin, respectively. Both nanoformulations had lower IC₅₀ values than pure artemisinin in cytotoxicity studies on MCF7 breast cancer cells, with the PEGylated version being somewhat more effective. Polyethylene glycol's increased effectiveness may be due to its increased permeability when PEGylated, according to the study's findings (Luís, Domingues, & Duarte, 2016). Dihydroartemisinin (DHA) has low oral bioavailability due to its peroxy link, which is highly vulnerable to light, heat, and oxygen. Amphiphilic block copolymeric micelles of MPEG5000-PLLA3200 loaded with DHA were synthesized using a more efficient solvent evaporation technique. Nanomicelles have a diameter of 130 nanometers or less on average. Human KB oral cancer and human hepatocyte L02 cells evaluated the freeze-dried micelles for cytotoxicity. For KB cell lines, IC₅₀ values for DHA copolymer micelle suspension and DHA suspension were 18.70 M. In contrast, DHA alone had an IC₅₀ value of 24.55 M. As with L02, DHACM showed no effect, demonstrating that Nano micelles were harmful to a wide range of cancer cell types (Matowa, Gundidza, Gwanzura, & Nhachi, 2020).

BERBERINE® nanoparticles were synthesized by Berberine Khemani and colleagues using PVA as a surfactant in a water-in-oil emulsion. When administered at an alkaline pH of 7.4, 50 percent of the anticancer medication Berberine was released during the first two hours when administered by nanoparticle delivery with a pH of 5.5, one of the most important discoveries. After that, Berberine was released 70% of the time. However, no additional releases were seen after that period had elapsed. Only 43% of the Berberine had been liberated after 72 hours at pH 7.4. Because Berberine is an alkaloid, researchers attributed its faster release in acidic environments (Mayzlish-Gati et al., 2018).

Lin et al. synthesized liposomal Berberine using a range of lipid compositions. To manufacture liposomes with a diameter of 121.6nm and an encapsulation efficacy of 14 percent, a thin film hydro/extrusion process and 5 percent PEG were used. Berberine liposomes were shown to have a greater IC50 on HepG2 cells than berberine solution, indicating that liposomes were more hazardous to the cells than the solution (Mbele, Hull, & Dlamini, 2017). In rats, Berberine's pharmacokinetics were examined. After that, a liposomal berberine injection was administered, and the drug was discovered 72 hours after the injection. Liposomes were able to extend circulation time in an animal model. However, the clearance of lipid-based Berberine from the circulation and tissues was also delayed (Miller & Snyder, 2012).

Combretastatin-A4

Nellamuthu et al. used liposomes that included hydrogenated soybean, cholesterol, and PEG-DSPE conjugates connected to PEG distal ends using RGD peptides (Arg-Gly-Asp). Liposomes with an entrapment rate of 80% and a diameter of 120 nm were used to load combretastatin A4. PEG-PLA micelles containing CA4 were coated with Arg-Gly-Asp peptides in another study. Micelles containing CA4 were able to encapsidate 14 percent of the time. Egg phosphatidylcholine, cholesterol, MPEG-DSPE, and CA4 were combined to generate liposomes containing CA4 (Muniyandi, George, Parimelazhagan, & Abrahamse, 2020).

Liposomes having a diameter of 342 nanometers were used to achieve encapsulation effectiveness of 48%. Unfortunately, the CA-4 delivery rate has fallen to roughly 80% after only 24 hours.

Lapachone

The *Tabebuiaimpetiginosa* canopy tree in the Amazon produces beta-lapachone. Beta-anti-cancer lap's properties have been related to NAD(P)H quinonoid reductase's two-electron reduction (NQO1). NQO1 enzymes, which convert quinones to hydroquinone forms, are found in colon, breast, pancreatic, and lung cancers. Beta-poor lap has a few applications due to its low water solubility of 0.038 mg/ml. Beta-lapachone was tested on tumors overexpressing NQO1 using PEG-PLA polymer micelles by Blanco et al. since beta-lap can selectively kill human cancer cells. Beta-lap micelles with a diameter of 29.6 nm were optimized using a film sonication technique (Nessa, Rahman, & Kabir, 2020). It has been shown that which-lap micelles are effective in killing cancer cells overexpressing the NQO1 gene ("NQO1+" and the "NQA-" form of the gene), as well as DU145 and H596 cells in an in vitro research on prostate, lung, and breast cancer. For the pharmacokinetics of these micelles, A549 subcutaneous lung tumor mice were also employed. If the micelles circulate for a lengthy period, it's conceivable that they'll accumulate in malignant tissues (Patel, 2016).

Technology-based Nanoparticles may be utilized to treat cancer

Several medicinal phytoconstituents and major components have cytotoxic action proposed in the classical period. Natural compounds are cancer-causing but not

cytotoxic in several studies. Several plant compounds, including polyphenols, alkaloids, phenolic acids, and flavonoids, are known to have medicinal properties. There are many different cytotoxic triterpenoids, including ursolic, avicin, and fomitelic acids. Animal studies show that flavonoids, such as myricetin and kaempferol have anticancer properties (Patil, Goyal, Sharma, Patil, & Ojha, 2015). Alkaloids like sanguinarine and matrine have also been found to have anticancer effects. The discovery of plant compounds or bioactive components that function as potential active ingredients or mechanisms of action may help traditional treatments. It is possible to combine these compounds with other plant chemicals. For example, antioxidation may help minimize disease-related damage, at least in part. To further understand how phytonutrients might enhance cancer risk, Liu studied many phytonutrients. Certain flavonoids were also investigated for their possible cancer-fighting properties. Various malignant cell lines are cytotoxic by specific plant bioactive phytochemicals. There is evidence that phytochemicals and plants have anti-cancer properties (Rahimian et al., 2021) (Figure 2).

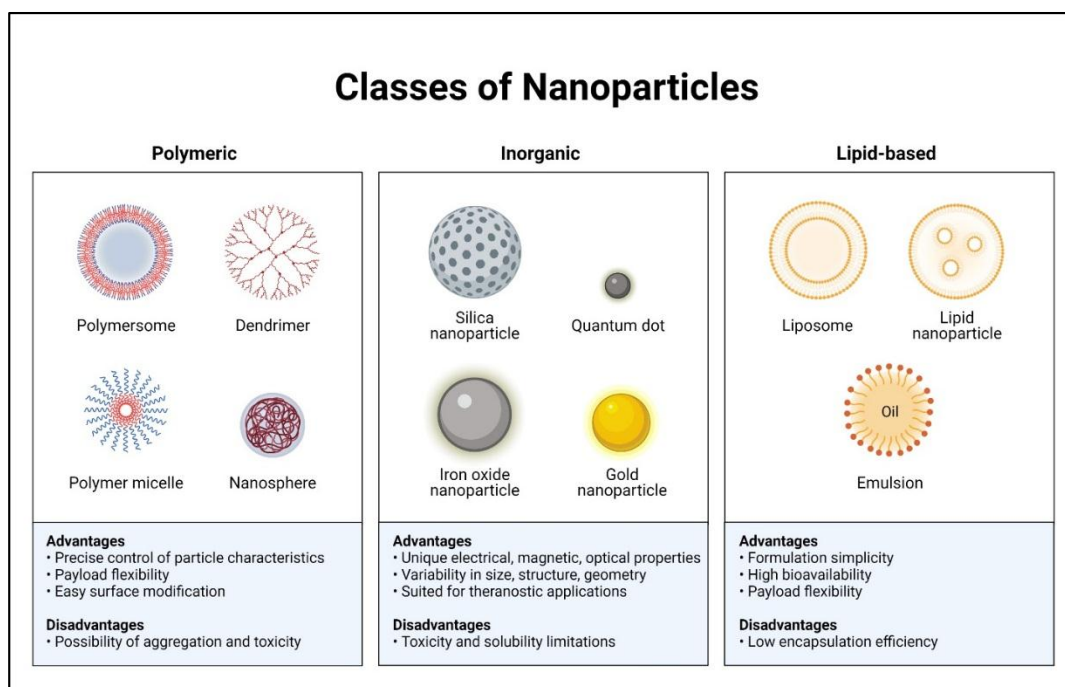


Figure 2: Classes of nanoparticles

Nanotechnology has the potential to transform the way we identify and treat cancer. Using nanoscales and bioengineering, researchers have found new ways to improve the safety and effectiveness of cancer treatment. Nanometer-scale structures are being investigated for a wide range of applications, including device design, industrial processes, and system architecture. Antibiotic resistance in tumors and longer intervals between doses in many modern cancer therapies mean that current cancer treatments face many challenges (Rahimian et al., 2021). For example, drugs for cancer may cause heart problems and decrease white blood cell counts. Other ways to bring nanoparticles to the target location

besides doxorubicin and daunorubicin administration and biocompatibility polymeric transport.

Understanding how nanoparticles fight cancer is a major focus of research

The appearance of necrosis and apoptosis in malignant cells may be used to discriminate between the two processes. Apoptotic cells have smaller nuclei and chromatin, and their cytoplasm appears to flow out of them. During intrinsic apoptosis, holes in the mitochondrial transmembrane depolarize the membrane. The receptor CD95 binds the Fas-associated death domain of the protein, and this binding promotes extrinsic apoptosis, resulting in a decrease in cellular ATP levels (FADD) (Raimi et al., 2021). By establishing the death complex, FADD links and stimulates caspase 8. The breakdown of nuclear and cellular membranes may lead to necrosis under extreme physiologic stress situations. The lipid bilayer in MGC803 cells completely ruptured after 24 hours of exposure to nanoparticles chitosan. This is a sure sign that someone has passed away. As a result, AuNPs were able to promote cancer growth in various ways. These included mechanical damage, photothermal disruption, and anticancer drug delivery with minimal tissue disruption. These nanoparticles use NADPH-dependent cell death signals to cause cell death. Regardless of whether or not ZnONP samples were reliant on Nrf2, researchers found that regardless of sample size or surface area, all samples produced DNA fragmentation in mouse macrophages surprisingly (Rajabi, Maresca, Yumashev, Chooapani, & Hajimehdipoor, 2021). ZnONP caused necrosis and death in macrophages because of their role in regulating immunological activation during inflammation. Nanoparticle-induced necrosis was seen in MGC803 cells, where the cytoplasm was disrupted, and organelles were left behind after necrosis. Cell death, DNA fragmentation, and nucleus shrinkage are all enhanced by ZnONP. Carbon nanoparticles administered to macrophages peroxidized lipids and released digestive enzymes, resulting in cell death. When membrane integrity is compromised, phagocytosis becomes less effective, DNA damage occurs, and cells may die (Ramprasath & Awad, 2015).

Treatment and diagnostics of cancer using Phyto-nano compounds

Nanomedicine has seen a significant shift in the last few years. Nanoparticles conjugated linked extract of plant anticancer drugs are more effective than conventional therapy because they can cross bio-membrane barriers because of their nanosize and surface reactivity. In the presence of X-rays, laser radiation, and ultraviolet light, nanodrug constructions can be used to treat surgically resistant malignant tumors or as contrast agents (Roy, Mukherjee, Sarkar, Mukherjee, & Biswas, 2015). FDA-approved nanoformulations of many anticancer medicines are now being tested on humans. There are several scenarios in which current licensed conventional medications may be used to create nanomedicines. Active and passive nanodrugs that break the cell cycle and promote cancer cell death will provide a novel, non-invasive technique to fight malignant tumors while decreasing their harmful effects. The nanodrug activates multiple signals and speeds up cancer cell death by inducing apoptosis as a ligand for receptors on the surfaces of cancer cells. Cancer reactivity is rare, but it does rely on effector reciprocity and is thus much more within our control (Salehi et al., 2019). Liposomes, dendrimers, metallic and nonmetallic nanoparticles, nanotubes, and

nanorods have influenced cancer pharmacology. It is possible that anti-neoplastic medications, when combined with phytomolecules, may pass through cell membranes and circumvent the immune system's defenses. Cancer cells are killed when their mitochondrial membrane potential collapses due to Phyto-nanocomposite entering the cytoplasm (Kazmi, Afzal, Gupta, & Anwar, 2012; Kumar Chellappan, Yenese, Chian Wei, & Gupta, 2017; Salehi et al., 2018).

Organic and semi-organic components

A combination of chemotherapy medicines and MDR modulators is being tested to treat multidrug resistance (MDR). Drugs like doxorubicin and taxanes may be less toxic thanks to the efflux pump P-glycoprotein 1 (P-gp), also known as multidrug resistance protein 1. Some forms of cancer have elevated levels of this gene's expression (e.g., liver, ovarian, pancreatic, and gastrointestinal). Therefore, Curcumin and other P-gp modulators, such as P-gp inhibitors, may improve the primary chemotherapy treatment's efficiency (Salmerón-Manzano, Garrido-Cardenas, & Manzano-Agugliaro, 2020).

According to Ganta et al., curcumin and paclitaxel nanoemulsions were made using flaxseed oil and lecithin as surfactants. In vitro, nanoemulsions of curcumin and paclitaxel had synergistic and additive effects on drug-resistant tumor cells. As a result, chemotherapy drugs are being tested with angiogenesis inhibitors. In addition, to keep nuclear nanoparticles safe, scientists created an envelope of PEGylated phospholipid block-copolymer (PLGA) (Gupta et al., 2019; Hemrajani et al., 2022; Samadi et al., 2020).

The chemotherapeutic drug Combretastatin A4 is present (doxorubicin). The writers were in favor of the time-sequenced delivery of medications. Combretastatin A4 and doxorubicin block the growth of the tumor's vascular system. By blocking the newly formed blood arteries in cancer, combretastatin A4 keeps DOX-encapsulated nanoparticles in situ (Seca & Pinto, 2018). Because the nano cell had a superior mix of drugs, it had synergistic additive effects. Drug combinations can work synergistically or additively depending on the ratio of the constituent components (Gupta et al., 2012; Hatware, Sharma, Patil, Rajput, & Gupta, 2020; Shaway, 2019).

Integrations and ligands, cell adhesion receptors, have transmembrane connections that activate various intracellular signaling pathways. These genes have been linked to the formation and development of malignant cells through overexpression in angiogenic arteries and tumor cells. For this reason, all successful therapeutic chemotherapy is focused on them. In dual drug, targeted delivery applications, Zhang et al. investigated the use of integrins and temporally sequenced drug release (Shin et al., 2018). RGD-ligand (cyclic arginine glycine aspartic acid tyrosin and lysine pentapeptide) was mechanically implanted in combretastatin A4 produced by Wang et al. and Yang using hydrophilic PEG functionalized by v3 RGD and an arginine-targeting Peptide (RGDyK) (Devi et al., 2018; Devkota et al., 2022; Shlyakhovenko, 2016).

To achieve an encapsulation efficiency of over 95%, pharmaceutical and micellar systems with particle diameters of 29.2 and 24.96 nm, respectively, were used as

the encapsulation vehicles. Micelles, in both cases, released drugs sequentially. In the first 24 hours after delivery, a large amount of DOX was created (around 20%), then released continuously for the following 20 days. A quarter of the time, CA4 was made available for download. In addition to DOX and CA-4, RGD liposome-modified liposomes included DOX and CA-4 (Slobodníková, Fialová, Rendeková, Kováč, & Mučaji, 2016). This is a major improvement over CA-4, which had a far slower release schedule. These targeted micelles or liposomes demonstrated remarkable effects in vitro and in B16-F10-carrying animals: enhanced intracellular drug absorption, dramatic tumor vasculature eradication, reduced tumor cell reproduction, and quick anti-proliferation/apoptotic induction (Dua, Gupta, Chellappan, Bebawy, & Collet, 2018; Dua, Gupta, Rao, & Bebawy, 2018; Subramaniam, Selvaduray, & Radhakrishnan, 2019).

Conclusions

Cancer has been treated and prevented for millennia using plant-derived compounds known as phytochemicals. But because of their low bioavailability, rapid metabolism, and lack of therapeutic use due to toxicity, safety, and dose, these compounds have yet to find a significant application in medicine. As a result of these difficulties, drug delivery methods have been improved to meet the needs of phytochemicals. They wanted to give an overall view of various phytochemical-nanocarrier systems, focusing on their release patterns and how well they had been packaged. They revealed that Nano formulations for cancer therapy might be made in many underdeveloped nations using their natural resources' phytochemicals.

Conflict of interest

There is no conflict of interest, the authors declare.

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