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Phytoconstituents Developed Nanoparticles for the Treatment of Cancer

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Abstract

One of the main sourses of death in the world is cancer. There are numerous medication classes available to treat various cancer kinds. At the moment, scientists are focusing a lot of effort on developing medications at the nanoscale level in order to lower their concentrations and improve target specificity. Nanostructures, nanomaterials, and nanoparticles are just a few of the many subdisciplines that make up the exciting and rapidly expanding science of nanotechnology. Because of these materials' size, shape, and possible effectiveness, they have become more well-known in science. As a result of the greater efficacy and fewer side effects of nanodrugs when compared to other commercial cancer drugs, the field of nanomedicine—which involves the use of various types of nanoparticles to treat cancer and cancerous cells—has gained significant traction. In this review, various medicinal plants and their active compounds are discussed in relation to their anticancer activities. Severe concerns about current chemotherapeutics are driving researchers to develop alternative therapeutics with better efficacy and safety

Keywords: Phytoconstituents, Nanoparticles, Cancer.

Introduction

Cancer is the second greatest cause of death worldwide, a significant public health concern, and one of the most common causes of illness and mortality overall. (1) Cancer is caused by damage of genes which control the growth and division of cells. Genes carry the instructions for basic functions of cells. (2) Blood is needed for cancerous cells to proliferate. It is possible to treat cancer by eliminating it, interrupting the blood flow to the cells, or changing the genes that cause the damage. Verifying the cell development allows for detection and diagnosis. As such, the required instruments need to be very sensitive. Researchers and scientists are hoping to use nanotechnology to develop therapeutic compounds that target particular cells and release the toxin in a controlled, time-released. (3) Developing single agents with the dual capabilities of cancer detection and therapeutic delivery is

the main goal. The nanoparticles will travel throughout the body, identify molecular alterations linked to cancer, help with imaging, release a therapeutic substance, and then track how well the intervention is working (4). It is possible to diagnose, cure, and confirm the growth of the cells. The destructive mechanism of the genes can be corrected, the blood supply to the cells can be cut off, or the cells can be destroyed. X-rays, CT scans, and MRIs are used to observe the physical growth or changes in the organ. A biopsy using cell culture is used to confirm the diagnosis of cancer. (3) Due to the fact that cells are only a few microns in size and nanoparticles (NP) are few nanometers in size, NP can penetrate cells and access DNA genes, potentially enabling the detection of gene defects.(5) Radiation therapy, chemotherapy, and surgery are the standard cancer treatment choices. In nanotechnology, certain nanoparticles (NPs) can be engineered to selectively absorb specific wavelengths of radiation, which, if they penetrate malignant cells, will cause them to burn. Therapeutic agents that target particular cells and deliver toxins to kill them can be created using nanotechnology. (6) Most people agree that cancer is a genetic disease that develops on its own cells and is caused by changes to the oncogene, tumor-suppressor, and genome-stability genes. But immunity, the stroma, and the tumor-cell microenvironment all play significant roles in cancer. Indeed, cancer cells must overcome both intrinsic (cell autonomous) and extrinsic (immune induced) hurdles to oncogenesis in order to progress to full-blown neoplasia. Tumor cells can only spread and ultimately destroy their host when they are able to subvert immune regulation.(7) Consequently, the notion that the immune system influences the development of tumors in humans is supported by the higher incidence of certain solid tumors in immunocompromised patients, reports of spontaneous tumor regression, and the favorable prognostic effect of tumor-specific cytotoxic T lymphocytes (CTLs) or antibodies (8). The NP will move throughout the body, identify molecular alterations linked to cancer, help with imaging, release a therapeutic substance, and then track how well the intervention is working. (9). Strong anticancer agents have historically been found in nature. These include the vinca alkaloids vincristine (VCR), vinblastine, vindesine, vinorelbine, taxanes paclitaxel (PTX), docetaxel], podophyllotoxin and its derivatives etoposide (ETP), teniposide], and a number of other medications that are derived from plants and that the US Food and Drug Administration (USFDA) has approved for use in cancer therapy. (10). Over thirty naturally occurring chemicals originating from plants have

been found and are currently undergoing clinical trials. Additional plant-derived chemicals that are presently being studied include combretastatin A4, homoharringtonine, β-lapachone, and flavopiridol. Synthetic flavone flavopiridol is made from the plant alkaloid rohitukine, which was extracted from Amoora rohituka's leaves and stems and then from Dysoxylum binectariferum.An inhibitor of cyclin-dependent kinase is flavopiridol. (11) This study focuses on novel plant-derived medicinal chemicals that have been shown in clinical studies to be effective in treating a variety of cancers (12).

Natural anticancer phytoconstituents

Presently, more than half of all anticancer medications licensed by the US FDA have natural origins, and more than 60% of all medications undergoing clinical trials for cancer have natural origins. Epidemiological research indicates that eating a diet high in phytochemicals, which includes fruits and vegetables, may lower one's chance of developing cancer (13). High concentrations of a wide variety of phytochemicals can be found in both fresh and processed fruits and food products. Polyphenols, which include anthocyanins and other flavonoids, hydrolysable tannins (ellagitannins and gallotannins), condensed tannins (proanthocyanidins), and other tannins, make up a significant component of these phytochemicals. Antioxidant is one of the proposed mechanisms by which polyphenols have anticancer effects (14).

One cannot undervalue the impact of natural ingredients on the development of anticancer drugs (15). About 60% of all medications presently undergoing clinical trials for various cancers are either natural products, compounds derived from natural products, pharmacophores derived from active natural products, or "old medicines in new clothing," indicating that natural compounds that have been altered have been connected to the targeting system. (16). We analyze almost 200 research that looked at the connection between eating fruits and vegetables and malignancies of the breast, colon, lung, cervix, esophagus, stomach, bladder, pancreas, and ovary.(17)

Human-consumed plants have thousands of phenolic chemicals in them. Due to dietary polyphenols' potential anticarcinogenic and antioxidant properties, their effects are currently of great interest. (6) Dietary polyphenols are thought to be anticarcinogens since they are antioxidants, yet there isn't enough concrete proof to support this theory. The inhibitory effects of phenolic acids and their

derivatives, tea and catechins, isoflavones and soy preparations, quercetin and other flavonoids, resveratrol, and lignans on cancer are reviewed in this chapter along with the processes underlying them, based on investigations conducted in vitro and in vivo (18). By altering the molecular processes at the beginning, promotion, and advancement phases of carcinogenesis, polyphenols may prevent it from occurring. Through their effects on estrogen-related activities, isoflavones and lignans may have an impact on the growth of tumors. Because the biological activity is determined by the tissue levels of the beneficial chemicals, there is a great deal of discussion over the bioavailability of dietary polyphenols (19).

Nanoparticles in cancer therapy

Nanoparticles (NPs) are described as particles having a single dimension of less than 100 nm with special characteristics that are often absent from bulk samples of the same substance. Nanoparticles can be categorized as 0D, 1D, 2D, or 3D depending on their general shape (20). The fundamental structure of nanoparticles is composed of three layers: the surface layer, the shell layer, and the core, which is commonly referred to as the NP itself and is essentially the central section of the NP. This basic composition is highly complex. Due to their remarkable characteristics, such as high surface-to-volume ratio, dissimilarity, sub-micron size, and improved targeting mechanism, these materials have become increasingly significant in interdisciplinary sciences.(21)

According to research, NPs can penetrate deep into tissues, increasing their permeability and retention capacity. Furthermore, the properties of the surface influence bioavailability and half-life by efficiently overcoming epithelial fenestration. As an illustration, nanoparticles coated with the hydrophilic polymer polyethylene glycol (PEG) reduce opsonization and evade T cell clearance (22). Furthermore, by adjusting the properties of particle polymers, it is feasible to maximize the rate of drug or active moiety release. In managing and treating cancer, the unique characteristics of NPs work together to control their therapeutic effect. In the last twenty years, a large number of therapies based on nanoparticles (NPs) have been released onto the market to help treat cancer (23). New potential for the production of NPs for a variety of therapeutic applications have been made possible by developments in nanotechnology and a growing awareness of the significance of nanoparticle features

(size, shape, and surface qualities) for biological interactions at the molecular level applications (24). The field of cancer diagnosis and treatment could undergo a revolution thanks to nanotechnology. Because tumor angiogenesis is poorly regulated, a tumor is frequently linked with a faulty, leaky vascular architecture. An appropriately engineered nanoparticulate system that enables passive targeting and allows nanocarriers filled with cytotoxic chemicals to build up in the tumor tissues will benefit from this EPR phenomenon (25). Drugs and drug delivery methods with modifications based on nanotechnology are being employed to treat cancer more and more frequently, with some even finding successful clinical applications. Improved cancer detection, more effective medication delivery to tumor cells, and molecularly tailored cancer therapy that enhances cancer patients' therapeutic management are all possible with nanotechnology (26,27). Currently, a lot of researchers are more interested in plant-based medicine delivery that uses nanotechnology to reach the tumor location more deeply. Because of their improved solubility and hence bioavailability, site-specific targetability, decreased toxicities, and possible synergistic efficacy against various neoplasms, nanoparticulate systems present a viable platform for efficient phytoconstitutional administration (28).

Three types of NPs are commonly utilized in drug delivery systems: hybrid, inorganic, and organic NPs.

Organic Nanoparticles

Polymeric Nanoparticles

It is generally known that polymeric nanoparticles (PNPs) are "colloidal macromolecules" with a particular structural architecture made of several monomers (29). Synthetic and natural polymers are utilized to prepare polymer nanoparticles, which constitute a substantial class of drug delivery vehicles. (21). Polymer nanoparticles are a versatile delivery system for a wide range of compounds, including as tiny chemicals, proteins, genes, and chemotherapeutic medicines. Poly(alkyl cyanoacrylate) (PACA), poly-caprolactone (PCL), polyanhydrides, polyethyleneimine (PEI), chitosan, gelatin, and polylactic acid (PLA) are just a few of the polymer nanoparticles that are being studied in the lab. To accomplish controlled drug release in the target, the drug is either encapsulated or bonded to the exterior of NPs, forming a nanosphere or a nanocapsule (30).

1 Solid Lipid Nanoparticles (SLN)

These are phospholipid monolayer, emulsifier, and water-based colloidal nanocarriers, with a size range of 1–100 nm. These are referred to as nanomaterials with zero dimensions. Triglycerides, fatty acids, waxes, steroids, and PEG are examples of the lipid component (31). Lipids have been proposed as an alternate carrier to circumvent these drawbacks of polymeric nanoparticles, especially for lipophilic drugs. Solid lipid nanoparticles (SLNs) are a class of lipid nanoparticles that are gaining a lot of attention from formulators all over the world (32).

Liposomes

These are spherical vesicles that contain pharmacological molecules encapsulated in phospholipids, which can be either unilamellar or multilamellar (33). 9 Liposomes have distinctive properties, including minimal intrinsic toxicity, minimal immunogenicity, and biological inertness (34). Following its description in 1965, 18 the first closed bilayer phospholipid structures, known as liposomes, were quickly suggested as methods of delivering drugs. Significant technological advancements including remote drug loading, extrusion for homogeneous size, long-circulating (PEGylated) liposomes, triggered release liposomes, liposomes containing nucleic acid polymers, ligand-targeted liposomes, and liposomes containing drug combinations were made possible by the groundbreaking work of innumerable liposome researchers over the course of nearly five decades (35).Because of their increased anti-tumor efficaciousness and improved absorption, liposomes offer a great vehicle for the administration of drugs including 1 doxorubicin, paclitaxel, and nucleic acid (36).

Dendrimers

Spherical polymeric macromolecules with a well-defined hyperbranched topology are called dendrimers. Dendrimers are characterized by highly branching architectures (37). Dendrimers typically have a size between 1 and 10 nm. Still, the size could be as much as 15 nm. A path 30 to synthetic target molecules with spherical shapes, distinct surface chemistries, and sizes that correspond to virus particles is provided by the dendrimer chemistry described. The biggest aim is a generation 13 dendrimer 1 made up of triazines connected by diamines, which is stable in the presence of additives and at different concentrations, pH levels, temperatures, and solvent polarity ranges (38).

A family of structurally defined macromolecules known as dendrimers has a central core, a high-density exterior that is terminated with surface functional groups, and a low-density inner made up of repeating branching units. Unlike their polymeric cousins, dendrimers are symmetrically structured and nanoscale particles that can be mass-produced in a reproducible manner using monodispersity technology (39).

Nanoemulsions

Colloidal NPs with heterogeneous mixes of an oil droplet in aqueous media with a diameter ranging from 10 to 1000 nm are known as nanoemulsions (40). Advanced melanoma can be treated with a nanoemulsion of rapamycin, bevacizumab, and temozolomide (41). In contrast to liposomes, nanoemulsions exhibit superior qualities, including stability, optical clarity, and biodegradability. In both cellular and animal models, the chosen medication combination loaded in IL shown encouraging results, most likely by influencing various mechanisms involved in tumor proliferation, dissemination, and angiogenesis. Future research would examine the impact of changing the chemical makeup of the nanoemulsion (42).

Inorganic Nanoparticles

Carbon Nanoparticles

As the name implies, carbon NPs are based on the element carbon. Since they are biocompatible and have optical, mechanical, and electrical qualities, they have been used extensively in the medical field. (43). The most promising options for various applications are the graphene family of nanomaterials because of their distinct intrinsic qualities, which are valued in their straightforward molecular design and their capacity to function in harmony with other nanomaterials already in existence (44). Via differentiation-based nanotherapy, graphene oxide may be a useful non-toxic therapeutic approach for eliminating cancer stem cells (45). A novel family of carbon compounds known as fullerenes (formerly buckminsterfullerenes) was first identified in 1985 (46). If fullerene (Cm) is deposited in the tumor tissue, it should have a photodynamic effect on the tumor since it efficiently produces singlet oxygen when exposed to light (47)

Metallic Nanoparticles

Since metallic nanoparticles have exceptional optical, magnetic, and photothermal capabilities, they are frequently investigated in "biological imaging" and targeted DDS. The most widely utilized metallic nanoparticles (NPs) include copper, silver, iron-based, and gold NPs. Because the size and surface characteristics of gold nanoparticles are easily manipulated, they are exploited as intracellular targeted drug carriers (48). The multidisciplinary topic of nanotechnology pertains to the engineering and design of items with a size less than 500 nanometers (nm). The National Cancer Institute has acknowledged that major advancements in cancer diagnosis and therapy can be achieved using nanotechnology, which presents an amazing and transformative opportunity. Nanotechnology has been researched and developed during the past few decades, mostly for application in cutting-edge medicine delivery systems (49). Most cancer-related deaths are caused by metastases. Treatment of metastases presents distinct challenges because to their tiny size, high multiplicity, and dispersion into various organ settings (50).

Quantum Dots

Semiconductor quantum dots (QDs) are light-emitting, nanoscale particles with special optical and electronic characteristics. These include the capacity to simultaneously excite multiple fluorescent colors, improved signal brightness, and stability of the fluorescent signal (37). In cultivated HeLa cells, quantum dots labeled with the protein transferrin underwent receptor-mediated endocytosis, while dots labeled with immunomolecules identified certain antibodies or antigens (51). The features of semiconducting quantum dots are highly uncommon; these particles are in the nanometer range. Band gaps in the quantum dots depend intricately on several aspects that are outlined in the article (52). A new family of inorganic fluorophores known as quantum dots (QDs) is becoming more well-known due to its remarkable photophysical characteristics (53). A targeted cancer imaging, treatment, and sensing system utilizing quantum dot (QD)−aptamer (Apt)−doxorubicin (Dox) conjugate [QD−Apt(Dox)] (54).

Magnetic Nanoparticles

MRI imaging often uses magnetic nanoparticles (NPs), and medication delivery involves metal or

metal oxides (55). Lipid-based gene transfection techniques and magnetic nanoparticles were used to induce active Fas expression in 43 breast cancer cells. Human Fas and GFP-expressing plasmid DNA (pDNA) was transfected into MCF-7 breast cancer cells (56). 14 When the tissues were injected with LHRH-SPIONs, the contrast enhancement of conventional T2 images acquired from the tumor tissue and of mice bearing breast cancer xenograft is demonstrated to be significantly greater than that in saline controls (57). 5 Breast cancer xenografts and lung metastases were also observed to have improved MRI contrast in magnetic anisotropy multi-CRAZED images of tissues taken from animals treated with SPIONs (58 59). 32 For the targeted treatment of oral squamous cell carcinoma, combining thermal ablation with antibody-targeting magnetic nanoparticles is a viable treatment option (60).

Hybrid 19 Nanoparticles

In order to overcome the limitations of single-component nanoparticles, improve properties, achieve new properties not achievable for single nanoparticles, and/or achieve multiple functionalities for single nanoparticles, hybrid nanoparticles are 44 constructed from at least two different nanoparticles. Various hybrid nanostructures, include Janus, dot-in-nanotube, dot-on-nanorod, heterodimer, core-shell, yolk-shell, and nanobranches (61). There are four different types of hybrid nanomaterials: mesoporous silica, gold, or 7 iron oxide nanoparticles combined with biodegradable polymers or biomacromolecuels to form inorganic nanoparticle/organic polymer composite systems; polysilsesquioxane (PSQ) nanoparticles synthesized from condensation of silanol-based monomers; and nanoscale coordination polymers (NCPs) and nanoscale metal-organic frameworks (NMOFs) composed of metal ions or clusters connected by organic linkers (62).

Hybrid nanoparticles based on two design methodologies (tanker vs. barge), where a nanoparticle's surface is coated with a nanotube system or contains liposomal, micellar, porous silica, polymeric, viral, noble metal, and nanotube systems. (63) We draw attention to the design elements that 2 must be taken into account to produce efficient nanodevices for the diagnosis and treatment of cancer (64,65).

1 Advantages of Nanoparticles in Cancer Therapy

A new era in cancer diagnosis, therapy, and management has been ushered in by the application of

nanotechnology. NPs increase the intracellular concentration of medications while avoiding harm in healthy tissue by active or passive targeting (66). One major concern for tumor therapy, particularly photodynamic therapy (PDT), has been targeted medication delivery. Our goal is to improve photosensitizer (PS) targeting efficiency 16 at the tumor site in vivo by employing folate-modified nanoparticles (NPs). (67).

3 Several studies have demonstrated that the trapping of anticancer medicines in submicronic colloidal systems (nanoparticles) can influence their distribution profiles in both tissues and cells. The goal of this strategy is to lessen systemic adverse effects while increasing antitumor efficacy (68). The nanoparticles are divided into three categories: (i) magnetite nanoparticles; (ii) various kinds of inorganic material-based nanoparticles that are typically utilized for medication 42 delivery, gene therapy, and other applications; and (iii) organic material-based nanoparticles (69). The advantage of using nanoparticles to target cancer is that they can do so passively, by simply building up and being lodged in tumors. The enhanced permeation 23 and retention effect, which is brought on by leaky angiogenetic arteries and inadequate lymphatic drainage, has been used to explain why tumors have higher ratios of macromolecules and nanoparticles than normal tissues (70).

1 Conclusion and Future Perspective

During the past 25 years, approximately 65% of anticancer medications have been developed from natural sources. Both 3 the preparation of their novel analogs and the large-scale supply of these naturally occurring chemicals have been made possible by partial or complete chemical synthesis. Nanotechnology offers the benefits of higher bioavailability, prolonged drug circulation duration, and multiple drug loading, all of which contribute to improved efficacy and decreased toxicity. Many of these chemicals suffer from low solubility and poor bioavailability. Numerous benefits come with these nanotechnology-based medicinal delivery systems, including their aqueous solubility, reduced toxicity, 1 biocompatibility, and surface modification amenability for related applications. The potential for utilizing nature-derived compounds in combination with nanotechnology to create drug delivery systems that target the tumor microenvironment and overcome multidrug resistance is enormous. When compared to traditional medications, NP-based DDS is associated with improved pharmacokinetics, biocompatibility, tumor targeting, and stability. Additionally, NPs offer a fantastic

platform for combination therapy, which aids in the eradication of MDR.

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