**Phytoconstituents Developed Nanoparticles for the Treatment of Cancer**

**Roshan yadav\*, Tejpal Yadav, Himmat Singh Chawara , Gaurav Dubey**

**Nims Institute of Pharmacy, Nims University Jaipur, Rajasthan-303121**

**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).

***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)**.** Liposomes have distinctive properties, including minimal intrinsic toxicity, minimal immunogenicity, and biological inertness (34). Following its description in 1965, 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 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 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 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 breast cancer cells. Human Fas and GFP-expressing plasmid DNA (pDNA) was transfected into MCF-7 breast cancer cells (56). 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). 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). For the targeted treatment of oral squamous cell carcinoma, combining thermal ablation with antibody-targeting magnetic nanoparticles is a viable treatment option (60).

**Hybrid 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 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 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 must be taken into account to produce efficient nanodevices for the diagnosis and treatment of cancer (64,65).

**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 at the tumor site in vivo by employing folate-modified nanoparticles (NPs). (67).

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 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 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).

**Conclusion and Future Perspective**

During the past 25 years, approximately 65% of anticancer medications have been developed from natural sources. Both 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, 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.

**Bibliography**

1. Molyneux G, Geyer FC, Magnay FA, McCarthy A, Kendrick H, Natrajan R, et al. BRCA1 basal-like breast cancers originate from luminal epithelial progenitors and not from basal stem cells. Cell Stem Cell. 2010 Sep 3;7(3):403–17.

2. Kumar P, Yadav N, Chaudhary B, Jain V, Balaramnavar VM, Alharbi KS, et al. Promises of phytochemical based nano drug delivery systems in the management of cancer. Chemico-Biological Interactions. 2022 Jan 5;351:109745.

3. Karpuz M, Silindir-Gunay M, Ozer AY. Current and Future Approaches for Effective Cancer Imaging and Treatment. Cancer Biother Radiopharm. 2018 Mar;33(2):39–51.

4. Mohanraj VJ, Chen Y. Nanoparticles - A review. Tropical Journal of Pharmaceutical Research. 2006;5(1):561–73.

5. Li C, Zhang J, Zu YJ, Nie SF, Cao J, Wang Q, et al. Biocompatible and biodegradable nanoparticles for enhancement of anti-cancer activities of phytochemicals. Chinese Journal of Natural Medicines. 2015 Sep 1;13(9):641–52.

6. Ravindran R. NANO TECHNOLOGY IN CANCER DIAGNOSIS AND TREATMENT: AN OVERVIEW. 2011;2(1).

7. Hertog MG, Hollman PC, Katan MB, Kromhout D. Intake of potentially anticarcinogenic flavonoids and their determinants in adults in The Netherlands. Nutr Cancer. 1993;20(1):21–9.

8. Zitvogel L, Apetoh L, Ghiringhelli F, Kroemer G. Immunological aspects of cancer chemotherapy. Nat Rev Immunol. 2008 Jan;8(1):59–73.

9. Nair HB, Sung B, Yadav VR, Kannappan R, Chaturvedi MM, Aggarwal BB. Delivery of antiinflammatory nutraceuticals by nanoparticles for the prevention and treatment of cancer. Biochemical Pharmacology. 2010 Dec 15;80(12):1833–43.

10. Bhanot A, Sharma R, Noolvi M. Natural sources as potential anti-cancer agents: A review. International Journal of Phytomedicine. 2011 Jan 1;3:09–26.

11. Afifi-Yazar FU, Kasabri V, Abu-Dahab R. Medicinal plants from Jordan in the treatment of cancer: traditional uses vs. in vitro and in vivo evaluations--part 1. Planta Med. 2011 Jul;77(11):1203–9.

12. Nobili S, Lippi D, Witort E, Donnini M, Bausi L, Mini E, et al. Natural compounds for cancer treatment and prevention. Pharmacol Res. 2009 Jun;59(6):365–78.

13. Asati V. Perspectives of Anti-Cancer Phytoconstituents in Pharmacotherapy. IJMPS [Internet]. 2022 [cited 2023 Dec 20];12(03). Available from: https://www.ijmps.org/uploads/181\_pdf.pdf

14. Coseri S. Natural products and their analogues as efficient anticancer drugs. Mini Rev Med Chem. 2009 May;9(5):560–71.

15. Potential phytochemicals in the fight against skin cancer: Current landscape and future perspectives - ScienceDirect [Internet]. [cited 2023 Dec 22]. Available from: https://www.sciencedirect.com/science/article/pii/S0753332218338538

16. Cragg GM, Newman DJ. Antineoplastic agents from natural sources: achievements and future directions. Expert Opin Investig Drugs. 2000 Dec;9(12):2783–97.

17. Block G, Patterson B, Subar A. Fruit, vegetables, and cancer prevention: a review of the epidemiological evidence. Nutr Cancer. 1992;18(1):1–29.

18. Almalki WH, Alotaibi NN, Alayaf AAM, Alotaibi AF, Althubiti MA. Phytochemical-based Nanodrug Delivery in Cancer Therapy. IJHS. 2022 Apr 24;(I):5736–54.

19. Yang CS, Landau JM, Huang MT, Newmark HL. Inhibition of carcinogenesis by dietary polyphenolic compounds. Annu Rev Nutr. 2001;21:381–406.

20. Laurent S, Forge D, Port M, Roch A, Robic C, Vander Elst L, et al. Magnetic iron oxide nanoparticles: synthesis, stabilization, vectorization, physicochemical characterizations, and biological applications. Chem Rev. 2008 Jun;108(6):2064–110.

21. Gavas S, Quazi S, Karpiński TM. Nanoparticles for Cancer Therapy: Current Progress and Challenges. Nanoscale Res Lett. 2021 Dec;16(1):173.

22. Shin WK, Cho J, Kannan AG, Lee YS, Kim DW. Cross-linked Composite Gel Polymer Electrolyte using Mesoporous Methacrylate-Functionalized SiO2 Nanoparticles for Lithium-Ion Polymer Batteries. Sci Rep. 2016 May 18;6:26332.

23. Prokop A, Davidson JM. Nanovehicular intracellular delivery systems. J Pharm Sci. 2008 Sep;97(9):3518–90.

24. Khan T, Gurav P. PhytoNanotechnology: Enhancing Delivery of Plant Based Anti-cancer Drugs. Frontiers in Pharmacology [Internet]. 2018 [cited 2023 Dec 22];8. Available from: https://www.frontiersin.org/articles/10.3389/fphar.2017.01002

25. Alshatwi AA, Athinarayanan J, Vaiyapuri Subbarayan P. Green synthesis of platinum nanoparticles that induce cell death and G2/M-phase cell cycle arrest in human cervical cancer cells. J Mater Sci: Mater Med. 2015 Jan 11;26(1):7.

26. Rao PV, Nallappan D, Madhavi K, Rahman S, Jun Wei L, Gan SH. Phytochemicals and Biogenic Metallic Nanoparticles as Anticancer Agents. Oxidative Medicine and Cellular Longevity. 2016;2016:1–15.

27. Capaldi Arruda SC, Diniz Silva AL, Moretto Galazzi R, Antunes Azevedo R, Zezzi Arruda MA. Nanoparticles applied to plant science: A review. Talanta. 2015 Jan 1;131:693–705.

28. Chaudhary KR, Banik P, Singh K. Recent trends in the delivery of plant-derived phytochemicals against various cancers using Nanotechnological approach: A comprehensive review. Journal of Drug Delivery Science and Technology. 2023 Sep 1;87:104859.

29. Samadian H, Hosseini-Nami S, Kamrava SK, Ghaznavi H, Shakeri-Zadeh A. Folate-conjugated gold nanoparticle as a new nanoplatform for targeted cancer therapy. J Cancer Res Clin Oncol. 2016 Nov;142(11):2217–29.

30. Amreddy N, Babu A, Muralidharan R, Panneerselvam J, Srivastava A, Ahmed R, et al. Recent Advances in Nanoparticle-Based Cancer Drug and Gene Delivery. Adv Cancer Res. 2018;137:115–70.

31. Mukherjee S, Ray S, Thakur RS. Solid Lipid Nanoparticles: A Modern Formulation Approach in Drug Delivery System. Indian J Pharm Sci. 2009;71(4):349–58.

32. Cavalli R, Caputo O, Gasco MR. Solid lipospheres of doxorubicin and idarubicin. International Journal of Pharmaceutics. 1993 Jan 1;89(1):R9–12.

33. Pegtel DM, Gould SJ. Exosomes. Annu Rev Biochem. 2019 Jun 20;88:487–514.

34. Samad A, Sultana Y, Aqil M. Liposomal drug delivery systems: an update review. Curr Drug Deliv. 2007 Oct;4(4):297–305.

35. Allen TM, Cullis PR. Liposomal drug delivery systems: from concept to clinical applications. Adv Drug Deliv Rev. 2013 Jan;65(1):36–48.

36. Zhang L, Gu FX, Chan JM, Wang AZ, Langer RS, Farokhzad OC. Nanoparticles in medicine: therapeutic applications and developments. Clin Pharmacol Ther. 2008 May;83(5):761–9.

37. Wang X, Yang L, Chen ZG, Shin DM. Application of nanotechnology in cancer therapy and imaging. CA Cancer J Clin. 2008;58(2):97–110.

38. Lim J, Kostiainen M, Maly J, da Costa VCP, Annunziata O, Pavan GM, et al. Synthesis of Large Dendrimers with the Dimensions of Small Viruses. J Am Chem Soc. 2013 Mar 27;135(12):4660–3.

39. Lo ST, Kumar A, Hsieh JT, Sun X. Dendrimer nanoscaffolds for potential theranostics of prostate cancer with a focus on radiochemistry. Mol Pharm. 2013 Mar 4;10(3):793–812.

40. Ma P, Dong X, Swadley CL, Gupte A, Leggas M, Ledebur HC, et al. Development of idarubicin and doxorubicin solid lipid nanoparticles to overcome Pgp-mediated multiple drug resistance in leukemia. J Biomed Nanotechnol. 2009 Apr;5(2):151–61.

41. Du M, Yang Z, Lu W, Wang B, Wang Q, Chen Z, et al. Design and development of spirulina polysaccharide-loaded nanoemulsions with improved the antitumor effects of paclitaxel. J Microencapsul. 2020 Sep;37(6):403–12.

42. Dianzani C, Monge C, Miglio G, Serpe L, Martina K, Cangemi L, et al. Nanoemulsions as Delivery Systems for Poly-Chemotherapy Aiming at Melanoma Treatment. Cancers (Basel). 2020 May 9;12(5):1198.

43. Swaminathan S, Pastero L, Serpe L, Trotta F, Vavia P, Aquilano D, et al. Cyclodextrin-based nanosponges encapsulating camptothecin: physicochemical characterization, stability and cytotoxicity. Eur J Pharm Biopharm. 2010 Feb;74(2):193–201.

44. Krishna KV, Ménard-Moyon C, Verma S, Bianco A. Graphene-based nanomaterials for nanobiotechnology and biomedical applications. Nanomedicine (Lond). 2013 Oct;8(10):1669–88.

45. Fiorillo M, Verre AF, Iliut M, Peiris-Pagés M, Ozsvari B, Gandara R, et al. Graphene oxide selectively targets cancer stem cells, across multiple tumor types: implications for non-toxic cancer treatment, via “differentiation-based nano-therapy.” Oncotarget. 2015 Feb 28;6(6):3553–62.

46. Mroz P, Tegos GP, Gali H, Wharton T, Sarna T, Hamblin MR. Photodynamic therapy with fullerenes. Photochem Photobiol Sci. 2007 Nov;6(11):1139–49.

47. Tabata Y, Murakami Y, Ikada Y. Photodynamic Effect of Polyethylene Glycol–modified Fullerene on Tumor. Jpn J Cancer Res. 1997 Nov;88(11):1108–16.

48. Mousa SA, Bharali DJ. Nanotechnology-Based Detection and Targeted Therapy in Cancer: Nano-Bio Paradigms and Applications. Cancers (Basel). 2011 Jul 15;3(3):2888–903.

49. Cuenca AG, Jiang H, Hochwald SN, Delano M, Cance WG, Grobmyer SR. Emerging implications of nanotechnology on cancer diagnostics and therapeutics. Cancer. 2006 Aug 1;107(3):459–66.

50. Schroeder A, Heller DA, Winslow MM, Dahlman JE, Pratt GW, Langer R, et al. Treating metastatic cancer with nanotechnology. Nat Rev Cancer. 2011 Dec 23;12(1):39–50.

51. Wc C, S N. Quantum dot bioconjugates for ultrasensitive nonisotopic detection. Science (New York, NY) [Internet]. 1998 Sep 25 [cited 2024 Jan 6];281(5385). Available from: https://pubmed.ncbi.nlm.nih.gov/9748158/

52. Bera D, Qian L, Tseng TK, Holloway PH. Quantum Dots and Their Multimodal Applications: A Review. Materials (Basel). 2010 Mar 24;3(4):2260–345.

53. Carrillo-Carrión C, Cárdenas S, Simonet BM, Valcárcel M. Quantum dots luminescence enhancement due to illumination with UV/Vis light. Chem Commun (Camb). 2009 Sep 21;(35):5214–26.

54. Bagalkot V, Zhang L, Levy-Nissenbaum E, Jon S, Kantoff PW, Langer R, et al. Quantum Dot−Aptamer Conjugates for Synchronous Cancer Imaging, Therapy, and Sensing of Drug Delivery Based on Bi-Fluorescence Resonance Energy Transfer. Nano Lett. 2007 Oct 1;7(10):3065–70.

55. Castaneda RT, Khurana A, Khan R, Daldrup-Link HE. Labeling stem cells with ferumoxytol, an FDA-approved iron oxide nanoparticle. J Vis Exp. 2011 Nov 4;(57):e3482.

56. Basoglu H, Goncu B, Akbas F. Magnetic nanoparticle-mediated gene therapy to induce Fas apoptosis pathway in breast cancer. Cancer Gene Ther. 2018 Jun;25(5–6):141–7.

57. Avval Z, Malekpour L, Raeisi F, Babapoor A, Mousavi SM, Hashemi SA, et al. Introduction of magnetic and supermagnetic nanoparticles in new approach of targeting drug delivery and cancer therapy application. Drug Metabolism Reviews. 2019 Nov 7;52.

58. Chariou PL, Ortega-Rivera OA, Steinmetz NF. Nanocarriers for the Delivery of Medical, Veterinary, and Agricultural Active Ingredients. ACS Nano. 2020 Mar 24;14(3):2678–701.

59. Meng J, Fan J, Galiana G, Branca RT, Clasen PL, Ma S, et al. LHRH-functionalized superparamagnetic iron oxide nanoparticles for breast cancer targeting and contrast enhancement in MRI. Materials Science and Engineering: C. 2009 May;29(4):1467–79.

60. Legge CJ, Colley HE, Lawson MA, Rawlings AE. Targeted magnetic nanoparticle hyperthermia for the treatment of oral cancer. J Oral Pathol Med. 2019 Oct;48(9):803–9.

61. Mohapatra S, Nguyen TA, Nguyen-Tri P, editors. Noble Metal-Metal Oxide Hybrid Nanoparticles [Internet]. Woodhead Publishing; 2019 [cited 2024 Jan 10]. p. 3–6. 62. He C, Lu J, Lin W. Hybrid nanoparticles for combination therapy of cancer. Journal of Controlled Release. 2015 Dec 10;219:224–36.

63. Huang X, El-Sayed IH, Qian W, El-Sayed MA. Cancer cell imaging and photothermal therapy in the near-infrared region by using gold nanorods. J Am Chem Soc. 2006 Feb 15;128(6):2115–20.

64. Corr SA, Rakovich YP, Gun’ko YK. Multifunctional magnetic-fluorescent nanocomposites for biomedical applications. Nanoscale Research Letters. 2008;3:87–104.

65. Sailor MJ, Park JH. Hybrid Nanoparticles for Detection and Treatment of Cancer. Advanced Materials. 2012;24(28):3779–802.

66. Rezvantalab S, Drude NI, Moraveji MK, Güvener N, Koons EK, Shi Y, et al. PLGA-Based Nanoparticles in Cancer Treatment. Front Pharmacol. 2018;9:1260.

67. Son J, Yang SM, Yi G, Roh YJ, Park H, Park JM, et al. Folate-modified PLGA nanoparticles for tumor-targeted delivery of pheophorbide a in vivo. Biochem Biophys Res Commun. 2018 Apr 6;498(3):523–8.

68. Brigger I, Dubernet C, Couvreur P. Nanoparticles in cancer therapy and diagnosis. Advanced Drug Delivery Reviews. 2012 Dec 1;64:24–36.

69. Fukumori Y, Ichikawa H. Nanoparticles for cancer therapy and diagnosis. Advanced Powder Technology. 2006 Jan 1;17(1):1–28.

70. Wang M, Thanou M. Targeting nanoparticles to cancer. Pharmacological Research. 2010 Aug 1;62(2):90–9.