



Metallic Nanoparticles from Natural Products as a Potential Anti-Cancer

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ABSTRACT

The complex system of human body has ever been under the scrutinizing set for the assessment for the proper functioning for yielding evidence for advanced quality of life. With the removal of each encumbrance of invading diseases, that has been questioning the existence of human nature; we are able advance the field of medical science to present a promising future for a suffering humankind. Lately Cancer has been a subject of special cognizance with its metastatic genetic effect, with alarming increase in mortality rate over past few years. The 2014 World Cancer Report states that, there are nearly 14 million new cancer cases and 8.2 million cancer-related deaths were reported in 2012. Since the 1960s, vetting of medicinal plants and their active constituents for various promising biological activities, such as anticancer activity, have been a major consideration. It is interesting to intensify the focus on the findings of medicinal plants, which have shown activity against various metabolic diseases like cancer.

Keywords: Anticancer, Nanoparticles, Metallic nanoparticles, Phytochemicals, Vinca Leaf, Tumour cells.

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INTRODUCTION

The complex system of human body has ever been under the scrutinizing set for the assessment for the proper functioning for yielding evidence for advanced quality of life. With the removal of each encumbrance of invading diseases, that has been questioning the existence of human nature; we are able advance the field of medical science to present a promising future for a suffering humankind. Lately Cancer has been a subject of special cognizance with its metastatic genetic effect, with alarming increase in mortality rate over past few years. The 2014 World Cancer Report states that, there are nearly 14 million new cancer cases and 8.2 million cancer-related deaths were reported in 2012¹. Within the span of next two decade, it is expected to have 70% increase new cancer cases². Africa, Asia, central and South America accounts epidemiologically 70% of all cancer deaths and 60% of the total new annual cancer cases around the world. In different types of cancer, lung cancer is associated with the highest mortality, followed by liver, and stomach cancer. Alongside, it is also interesting

to note that there is an extensive option availed for cancer therapy¹. One among the prominent choice of treatment, the Chemotherapy i.e., treatment with drugs, is utilized with the combination of cytotoxic agents. Nevertheless, various undesirable side effects like multidrug resistance (MDR) are linked with these cytotoxic drugs³.

To annihilate the undesirable effects of chemotherapy alone or with the combination of cytotoxic drugs or radiation therapy, cancer research has been shifting its focus towards the investigation of the potential antitumor activities of plant extracts. Natural compounds isolated from medicinal plants are believed to be promising leads in the development of anticancer drugs. Since the 1960s, vetting of medicinal plants and their active constituents for various promising biological activities, such as anticancer activity, have been a major consideration⁴. It is interesting to intensify the focus on the findings of medicinal plants, which have shown activity against various metabolic diseases like cancer.

Nanoparticles: An Overview

A matter particle with the size measurement between 01 and 100 nm in diameter can be defined as a nanoparticle (NP)- a subclass of colloidal particle⁵, which is also referred for larger particles, up to 500 nm, or fibers and tubes that are less than 100 nm⁶. Being much smaller than the wavelengths of visible light (400-700 nm), needing the use of electron microscopes to see nanoparticles which cannot be seen with ordinary optical microscopes. This helps in dispersions of nanoparticles in



transparent media to be transparent, whereas suspensions of larger particles usually scatter some or all visible light incident on them. Common filters such as a common ceramic candles can be easily used to pass the nanoparticles which on other hand requires special Nano filtration techniques for separation from liquids⁷. NPs usually have a large surface to volume ratio and the properties of that surface layer may dominate over those of the bulk material. This effect is particularly strong for nanoparticles dispersed in a medium containing different compositions, since the interactions between the two materials at their interface also becomes significant. NPs occur widely in nature and are objects of study in many sciences such as chemistry, physics, geology and biology. Being at the transition between bulk materials and atomic or molecular structures, they often exhibit phenomena that are not observed at either scale. The production of NPs is an important branch of nanotechnology.

Different types of nanoparticles

Different types of nanoparticles are classified with respect to their differing structure, shape, size and physio-chemical properties. Some to be noted are carbon-based nanoparticles, semiconductor nanoparticles, ceramic nanoparticles, metal nanoparticles, polymeric nanoparticles and lipid-based nanoparticles.

Carbon-Based Nanoparticles

Carbon nanotubes (CNTs) and fullerenes are the two main components of carbon-based nanoparticles. CNTs are graphene sheets rolled into a tube and are mainly used for the structural reinforcement as they are much stronger than steel. CNTs are of two type: single-walled carbon nanotubes (SWCNTs) as well as the multi-walled carbon nanotubes (MWCNTs)⁸. CNTs are unique for their thermally conductive property along the length and non-conductive across the tube. The allotropes of carbon having a structure of hollow cage of sixty or more carbon atoms are the known as Fullerenes⁸. The structure of which looks like a hollow football. The carbon units of C-60 Buckminsterfullerene structures have a pentagonal and hexagonal arrangement. Due to their electrical conductivity, structure, high strength, and electron affinity they are widely used for commercial purpose

Ceramic Nanoparticles

Inorganic solids made up of oxides, carbides, carbonates and phosphates are ceramic NPs⁹. These nanoparticles have high heat resistance and chemical inertness with applications in photo catalysis, photo degradation of dyes, drug delivery, and imaging.

They perform as a good drug delivery agent by altering some of the characteristics of ceramic NPs like size, surface area, porosity, surface to volume ratio, etc.,. These nanoparticles have medical applications such as an effective drug delivery system for a number of diseases like bacterial infections, glaucoma, cancer, etc.

Metallic Nanoparticles

Metal NPs are prepared from metal precursors by chemical, electrochemical, or photochemical methods¹⁰. By reducing the metal-ion precursors in solution by chemical reducing agents, these metal nanoparticles can be synthesized by chemical methods, which have the ability to adsorb small molecules and have high surface energy. They have been used in research areas, detection, imaging of biomolecules and in environmental, and bioanalytical applications. For example, before analyzing in scanning electron microscopy (SEM), gold nanoparticles are used to coat the sample. This enhance the electronic stream, which help to get high quality SEM images.

Polymeric Nanoparticles

Polymeric NPs are organic material based structures having the shape like Nano capsular or Nano spheres varying as the method of preparation varies¹¹. The structure of Nano sphere is like a matrix whereas the Nano capsular particle has core-shell morphology. In the former, the active compounds and the polymer are uniformly dispersed whereas in the later the active compounds are surrounded by a polymer shell.

Some of the merits of polymeric NPs are controlled release, protection of drug molecules, ability to combine therapy and imaging, specific targeting and many more. They have applications in drug delivery and diagnostics. The drug deliveries with polymeric nanoparticles are highly biodegradable and biocompatible.

Lipid-Based Nanoparticles

The spherical shaped Lipidic NPs have a diameter ranging from 10 to 100 nm with a solid core made of lipid and a matrix. This contains soluble lipophilic molecule along with the external core of these nanoparticles is stabilized by surfactants and emulsifiers¹². Having a wide application in the biomedical field as a drug carrier and delivery agent, they are also widely used in the RNA release in cancer therapy.

Green Synthesis of Nanoparticles

Various classes of alkaloids and flavonoids have been isolated from several medicinal plants and have shown promising efficacy against numerous types of cancerous cells both in vitro and in vivo. As of now, researchers have focused only on rapidly acting metallic nanoparticles, which have been recognized to have unique physiochemical properties attributing to many biomedical advancements. Of commonly used metallic nanoparticles, silver and gold are the prominent ions in utilized for the green synthesis of NPs.



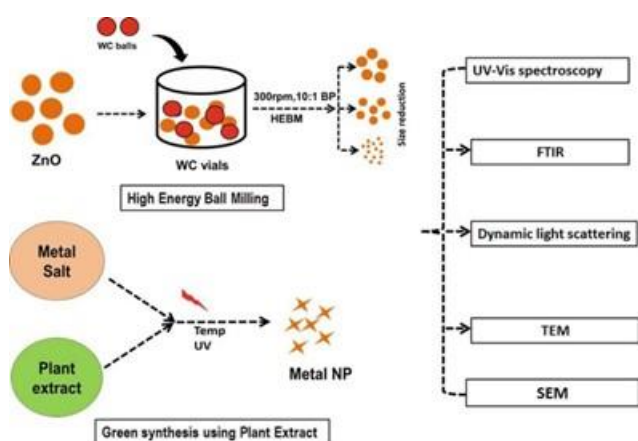


Figure 1: General scheme for green synthesis of nanoparticles

General Pathophysiology of Cancer

A disease of uncontrolled cell division and tissue growth regulation, cancer transforms a normal cell into a tumor cell by affecting the gene regulation of human system. To regulate the normal balance of cell growth, the human system has two constituent genes called as Oncogenes and Tumor suppressor genes. Owing to the property of promoting cell growth and production, Oncogenes are genes that promote cell growth and reproduction whereas the tumor suppressor genes are genes that inhibit cell division¹³. Malignancy can be resulted from either uncontrolled formation of new oncogenes or inappropriate over-expression of oncogenes, or tumor suppressor genes under-expression. Changes in multiple genes usually leads normal cell transforming to a malignant one. These genetic changes occur at different level and by mechanism. More common error at genetic level are alteration in the nucleotide sequence of DNA genome. The deletion or gain of a large portion of a chromosome leads to huge mutations. Also, it is interesting to note that the genomic amplification (when a cell gains copies of a one or more oncogenes at small chromosomal locus) and translocation (abnormal fusion of two separate chromosomal regions) leading to the onset of cancer. Genomic material from a DNA virus or retrovirus integration leads to disruption of normal human gene set¹³. Apoptosis is the self-destruction method of a severely damaged cell through complex process for protecting from malfunctioning. The failure to combat the mutations can lead to formation of progeny mutant cells that can severely propagate which can eventually lead to formation of immortal cells than its normal counterpart¹⁴. Further mutations can also send error signals to nearby cells. These can be caused due to disruptive substances known as carcinogens.

This rebellion-like scenario is an unacceptable 'survival of the fittest' in which evolutionary driving forces function against the nature and implementation of order by the body. Initiated by unregulated mutation, clonal evolution leads to more invasive stages, disrupting the architecture and order of the body¹⁵. Clonal evolution results in heterogeneity of the intra-tumor (cancer cells with heterogeneous mutations) that complicates the

implementation of successful methods for treatment. Evasion of apoptosis, self-sufficiency in growth signals, insensitivity to anti-growth signals, persistent angiogenesis, infinite replication capacity, metastasis, reprogramming of energy metabolism and evasion of immune destruction are classified into the characteristic capabilities established by cancers¹⁶.

Role of Phytochemicals in Cancer

As the effect of numerous extracts from medicinal plants have reported that medicinal plants display anticancer and cytotoxic activities^{17,18}. Polyphenols derived from medicinal plants notably possess huge biological potential. These polyphenols usually are phenolic acids, flavonoids, terpenes, and alkaloids. Triterpenoids such as ursolic acid have been reported to possess cytotoxic effects whereas flavonoids such as kaempferol and alkaloids such as matrine and sanguinarine have studies showing anticancer properties¹⁸. The mechanisms of action of medicinal plants and their active ingredients have reportedly demonstrated through major mechanism of intrinsic antioxidant activity. Numerous phytochemicals present in medicinal plants can induce cytotoxicity activity¹⁸.

Role of Metallic Nanoparticles in Cancer

Natural Phytoconstituents can be formulated with nanoparticles in many innovative ways that increases scope in treating cancer

Silver Nanoparticles

Silver nanoparticles known for highest thermal and electrical conductivity, play an important role for biological activities such as antibacterial, antifungal, antiviral, and anti-inflammatory activities. AgNPs have remarkable cytotoxic potential and is extensively studied in cancer research. Currently, many researchers are focusing on green-synthesized nanoparticles from medicinal plants to investigate various biological efficacies namely their antimicrobial, anticancer, antidiabetic, and antimalarial properties. Generally, the cytotoxicity of AgNPs against cancerous cells tends to increase with their concentration¹⁹.

Gold Nanoparticles

The gold nanoparticles exist in a non-oxidised state whereas oxidation states of gold exist in auroous and auric compound. Several researchers have suggested many techniques including transmission electron microscopy and atomic force microscopy which helps in direct imaging of gold nanoparticles. In the 19th century, in the scientific paper of Michael Faraday, he describes the production of colloidal gold by the reduction of aurochloric acid by phosphorous²⁰. When the properties such as size and surface coating are controlled, we could use gold nanoparticles with medical application. In recent years been an explosion

in AuNPs research ¹⁰.

Iron Oxide Nanoparticles

Iron oxide nanoparticles have effectively shown antitumor activity via direct and indirect mechanism of action. They usually act through nontoxic wavelength like near infrared radiation. The reactive oxygen species (ROS) can be transformed from radiant energy from iron oxide to decrease the adverse effects to healthy tissues and cells, thus the iron oxides can bind covalently to the tumor site by its particulate property ²¹.

There are specially designed nanoparticles with properties specifically characterizing to the shape of iron oxide. Especially the spherically shaped iron oxide nanoparticles were endorsed to treat prostate cancer as well as to induce magnetic tumor hyperthermia in the brain along with other suggestive therapies ²¹. There are wide therapies with iron oxides nanoparticles for treating tumor cells that includes hyper thermic therapy. Nanomaterials receive energy from external source which can kill the tumor cells.

Titanium Dioxide Nanoparticles

Titanium oxide NPs can be surface-engineered to inhibit tumor growth. They can play potentially important roles in the medicinal industry. However, scope of rigorous risk-benefit analysis is still there ²².

Cerium Oxide Nanoparticles

Cerium oxide NPs are able to directly limit the growth of irradiated cancer cells due to oxidative stress and radiation-induced harm without affecting the surrounding tissue. Without damaging normal tissues, these NPs can selectively induce apoptosis and high levels of oxidative stress in cancer cells ²³. In addition, the application of nanoparticles of cerium oxide can contribute to DNA damage, resulting in the death of cancer cells. The levels of reactive oxygen species in tumour cells are increased by cerium oxide nanoparticles, leading to apoptosis but do not exert genotoxic effects ²³. The antitumor activity of nanoparticles of cerium oxide depends greatly on their size and shape, while DNA damage in tumour cells is caused by both small and large nanoparticles.

Zinc Oxide Nanoparticles

Nano-sized ZnO particles with a diameter of less than 100 nm are ZnO NPs. These nanoparticles can be designed by using various methods such as solid, liquid and gaseous ²⁴. The only fruitful use of the synthesis of nano particles is that they can once again be conveniently aggregated into macro-sizes. Therefore, surfactants, polymer molecules, or other organic molecules attached to the surface of NPs, such as triton-X 100 or polyethylene glycols, (PEG) are stabilised. The key importance of nanoparticles is that reducing their size to nanoscale will lead to developing a new physical-chemical, structural, electronic and magnetic properties, which are unique in nature. These novel properties, are mainly responsible for the special

and comprehensive biological and medical application of nanoparticles ²⁴. ZnO NPs now have a broad variety of cancer therapy applications, bio-sensing devices, drug/gene delivery, biological mimetic nano machines, etc.

Bimetallic Nanoparticles

A mixture of different metals can generate significant cytotoxic effects on the cancer cells, in addition to single metal nanoparticles. The bimetallic NPs synthesised with quercetine and gallic acid in silver-selenium (Ag-Se) exhibited potential application of anti-tumor activity in Dalton lymphoma cells ²⁵. The toxicity of AgNPs and AuNPs against various cancers and tumours in vitro and in vivo has been extensively tested. However, researchers have succeeded in developing alloys of these two noble metals with greatly increased expertise in the field. In both cases, these nanocomposites can be synthesised; colloidal particles are coated with Ag-coated Au and/or Au. It can be achieved easily with one metal salt reduction.

Role of Bacteria in Metallic Nanoparticle Synthesis

The bacteria are able to reduce heavy metal ions amazingly and are one of the strongest NP synthesis choices. In some bacterial species, for instance, stresses such as toxicity of heavy metals or metals could be settled by means of complex protection mechanisms. It was observed that some of them could survive and grow even at high metal ion concentrations (e.g., *Pseudomonas stutzeri* and *Pseudomonas aeruginosa*). *T. thiooxidans* is able to reduce ferric iron at low pH medium aerobically. Mullen et al. examined the ability of *Bacillus cereus*,

B. subtilis, *E. coli*, and *P. aeruginosa* for removing Ag⁺, Cd²⁺, Cu²⁺, and La³⁺ from solution. They found that bacterial cells were capable of binding large quantities of metallic cations.

Targeting Tumor Cells with Metallic Nanoparticles

The targeted delivery of therapeutic agents to tumor cells is a challenge as most of the agents distribute to the whole body non specifically resulting in general toxicity. For a significant number of applications in different fields of medical treatment, metallic nanoparticles have been used. In cancer treatment, metallic NPs are emerging as new carriers and contrast agents. These metallic nPs were used for active and passive specific purposes ²⁵. Prolonging the survival time and increasing the quality of life of the patient should be the ultimate aim of anticancer therapy. Recent development has opened the way for the targeting and distribution of drugs unique at the site.



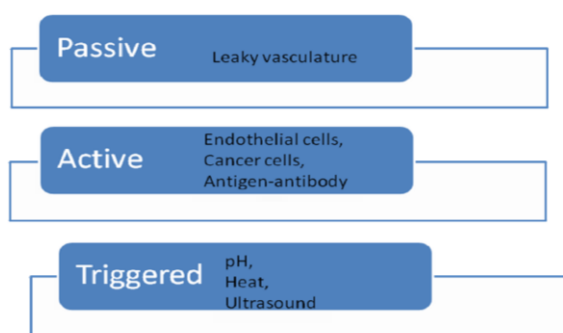


Figure 2: Targeting strategies

Metallic NPs for drug delivery are solid colloidal particles ranging in size from 10 to 1000 nm that contain a therapeutic agent. Metallic NPs contain specific ligands that bind with particular tumor cells²⁵. In this way, metallic nanoparticle drug delivery systems are capable of sequestering anticancer drugs exclusively within the tumor and thereby reduce the accumulation of drugs to healthy organs. They can target tumors through antigen-dependent (specific) or antigen independent (nonspecific) mechanisms. Metallic NPs are used to manipulate not only the size of drug particles but also the physical characteristics, and thus the extent and target of drug delivery. Owing to the potential to carry a large dose of drug along with targeting specificity, metallic NPs can deliver high concentration of anticancer drugs at the desired site, thus avoiding toxicity and other side effects²⁵. Their application is also widening in cancer diagnosis.

Application of Phytoconstituent Loaded Metallic Nanoparticles as Anticancer Agents

AuNPs and AgNPs have shown great capabilities and promising results in both cancer diagnostics and therapeutics. The application of metallic NPs offers such advantages over traditional therapy; the medications commonly used for anti-cancer therapies are toxic to the body, causing side effects and unintentional or untargeted effects on normal body physiology, drug resistance growth, rapid drug metabolism, and the patient's body clearance decreasing successful care. Metal NPs are biologically synthesized to produce safe and efficient cancer therapeutics. NPs made from various metals can have different characteristics and thus various toxicity mechanisms for various cancer cells should be predicted. In conjugation or combination with medications, AuNPs and AgNPs may also be used or coated with a polymer to be used against cancer cells.

Curcumin

Curcumin (from *Curcuma longa*). Natural phenols that are responsible for the yellow colour of turmeric are the main curcuminoids. The treatment of different cancers including myeloma, pancreas and colon and psoriasis, with curcumin, has been reported. A green chemistry method was used to synthesise the gold nanoparticles²⁵. By using curcumin as a reducing and stabilising agent the gold nanoparticles have been created. Using sodium carbonate,

0.11 g of curcumin was dissolved in 15 ml of dimethylsulphoxide and the pH of the solution increased to 9.3. With 2 ml of curcumin, 1 mM of HAuCl₄ was applied dropwise with shaking until the colour shifts from yellow to colourless, black and burgundy red. Curcumin conjugated auNPs are produced by six stages: deprotonation, decrease, nucleation, development, cleaving and ripening. AgNPs have been developed using the method of chemical reduction. In 500 ml of distilled water, 84.9 mg silver nitrate has been dissolved. Shooked and heated the solution to boil temperature and added 5 ml trisodium citrate (1 g dissolved in 100 ml of water). The solution was left for 2 hours to boil and the colour was changed to greenish²⁵. This reaction reduces trisodium citrate to silver nitrate to form AgNPs

Camptothecin

Camptothecin is a cytotoxic quinolone alkaloid that isolates *Camptotheca acuminata* from the bark and stem. By targeting the nuclear enzyme topoisomerase I, camptothecin and its derivatives inhibit religation of cleaved, single-stranded DNA. This finally leads to replication inhibition, and there is cell death. Camptothecin-loaded gold nanomaterials were synthesised under a strong basic condition by the sodium borohydride reduction method²⁶. TEM, AFM and UV-vis spectroscopy have characterised the obtained gold nanomaterials. The colloidal solution of camptothecin was very stable and can be kept at room temperature for more than two months with no noticeable changes.

Pomegranate Extract

Pomegranate extracts selectively inhibit production of both the plates of the culture and the mouse xenograft model of the breast, uterus, colon, lung and skin tumours. The inconsistency and low bioavailability of pomegranate extracts and their active ingredients are a major concern. Nanotechnology can solve this problem by concealing the active ingredient within the nanoparticle system to prevent further degradation and to improve bioavailability²⁶. A fruit-bearing, cabbage shrub from the Lythraceae family is the pomegranate (*Punica granatum*). Pomegranate fruits are antioxidant and are used for baking, cooking and juice mixtures, smoothies and alcoholic drinking and are widely used for meal trimmings. The AuNPs synthesis was based on pomegranate juice and peel extracts as reducing and stabilising agents.

Vinca Leaf

Vinca (*Catharanthus roseus*) contains vincristine and vinblastine. They exert their activity by preventing polymerization assembly of microtubules. Liu et al (2015) designed and formulated vincristine sulphate loaded AgNPs, which were found to be active against acute leukemia and thyroid cancer²⁶. The same research group formulated vinblastine loaded AgNP which displayed anti-tumor activity in bladder cancer²⁶.

Indian Cress

Indian cress (*Tropaeolum majus*) is a plant from Tropaeolaceae family. Green synthesized AgNPs from leaf extract of Indian cress have been found to possess anticancer activity²⁷. Face centred cubic nanocrystals were formed which displayed efficient anticancer activity against MCF7 cell line and VERO cell line.

Yellow Bell Orchid

Yellow bell orchid i.e. *Bauhinia tomentosa* is a popular plant in tropical countries. AuNPs loaded with leaf extract of the same have been prepared and studied by Mukundan et al²⁷. In the experiment, AuNPs of average diameter 31.32 nm showed significant anticancer activity against laryngeal HEP-2 carcinoma cells.

Brown seaweed

Sargassum wightii is a brown seaweed possessing multiple pharmacological activities. Aqueous extract of this carotenoid rich seaweed was formulated into magnesium NP (MgONP) by green synthesis method²⁸. Prepared NPs exhibited potent anticancer activity in A549 cell line probably by inducing ROS mediated apoptosis rising hope for future clinical use to treat different types of carcinomas.

Indian Coleus

Coleus forskohlii is widely used in ancient systems of medicine. AuNPs and AgNPs were formulated with extracts of *C. forskohlii* and examined for pharmacological activity²⁸. Prepared NPs were found to possess anti-tumor activity against HEPG2 liver cancer cell lines.

CONCLUSION AND FUTURE SCOPE

As innovative and novel discoveries for better medical care are increasing in demand and much appreciated in an era of rapidly growing health system, the scope of a better health care system arises from inculcating nanotechnology with medicine. Such an innovative yet effective technique is involving the nanoparticles use in cancer therapy. The biological synthesis of NPs using several components of medicinal plants has reduced side effect when compared to other commercial drugs. As of now, there are few Nano-based clinical cancer treatments and few which are under the pipeline of development.

A reliable and ecofriendly process of synthesizing and inculcating metallic nanoparticles for the treatment of cancer is a need of hour. The deep understanding of mechanism of biological, chemical, molecular mechanism of nanoparticle synthesis as well as use of phytoconstituents then becomes essential. With different methods of formulation like conjugation, drug encapsulation Metallic nanoparticles can be formulated, which make them potential candidates for cancer-specific and patient-specific treatments. But the research needs to be routed and rooted in a right way and needs to be focused than ever before. Surely the effective application of phytochemical-loaded metallic nanoparticles as

anticancer agents is promising in the area of research and medicine.

REFERENCES

1. Stewart BW, Wild CP. World cancer report 2014. IARC. IARC Nonserial Publ: Lyon, France. 2014;630.
2. Ghouri YA, Mian I, Rowe JH. Review of hepatocellular carcinoma: Epidemiology, etiology, and carcinogenesis. *Journal of carcinogenesis*. 2017;16. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/pmc5490340/>
3. Markman JL, Rekechenetskiy A, Holler E, Ljubimova JY. Nanomedicine therapeutic approaches to overcome cancer drug resistance. *Advanced drug delivery reviews*. 2013 Nov 30;65(13-14):1866-79. Available from: <https://www.sciencedirect.com/science/article/pii/S0169409X13002329>
4. Phillipson JD. 50 years of medicinal plant research-every progress in methodology is a progress in science. *Planta medica*. 2003 Jun;69(06):491-5. Available from: <https://dnb.info/1176524771/34>
5. Auffan M, Rose J, Bottero JY, Lowry GV, Jolivet JP, Wiesner MR. Towards a definition of inorganic nanoparticles from an environmental, health and safety perspective. *Nature nanotechnology*. 2009 Oct;4(10):634-41. Available from: <https://www.nature.com/nnano/journal/v4/n10/abs/nnano.2009.242.html>
6. Arruda SC, Silva AL, Galazzi RM, Azevedo RA, Arruda MA. Nanoparticles applied to plant science: A review. *Talanta*. 2015 Jan 1;131:693-705. Available from: <https://www.sciencedirect.com/science/article/pii/S0039914014007309>
7. Patil AS, inventor; Microban Products Co, assignee. Bacteriostatic filter cartridge. United States patent US 6,854,601. 2005 Feb 15. Available from: <https://patents.google.com/patent/US6854601B2/en>
8. Jia Y, He L, Kong L, Liu J, Guo Z, Meng F, Luo T, Li M, Liu J. Synthesis of close-packed multi-walled carbon nanotube bundles using Mo as catalyst. *Carbon*. 2009 Jun 1;47(7):1652-8. Available from: <https://www.sciencedirect.com/science/article/pii/S000862230900955>
9. C Thomas S, Kumar Mishra P, Talegaonkar S. Ceramic nanoparticles: fabrication methods and applications in drug delivery. *Current pharmaceutical design*. 2015 Dec 1;21(42):6165-88. Available from: <https://www.ingentaconnect.com/content/ben/cpd/2015/00000021/00000042/art00011>
10. Rai M, Ingle AP, Birla S, Yadav A, Santos CA. Strategic role of selected noble metal nanoparticles in medicine. *Critical reviews in microbiology*. 2016 Sep 2;42(5):696-719. Available from: <https://www.tandfonline.com/doi/abs/10.3109/1040841X.2015.1018131>
11. Letchford K, Burt H. A review of the formation and classification of amphiphilic block copolymer nanoparticulate structures: micelles, nanospheres, nanocapsules and polymersomes. *European journal of pharmaceutics and biopharmaceutics*. 2007 Mar 1;65(3):259-69. Available from:



<https://www.sciencedirect.com/science/article/pii/S0939641106003316>

12. Das S, Chaudhury A. Recent advances in lipid nanoparticle formulations with solid matrix for oral drug delivery. *Aaps Pharmscitech*. 2011 Mar;12(1):62-76. Available from: <https://link.springer.com/article/10.1208/s12249-010-9563-0>
13. Klein G. The role of gene dosage and genetic transpositions in carcinogenesis. *Nature*. 1981 Nov;294(5839):313-8. Available from: <https://www.nature.com/articles/294313a0>
14. Lengauer C, Kinzler KW, Vogelstein B. Genetic instabilities in human cancers. *Nature*. 1998 Dec;396(6712):643-9. Available from: <https://www.nature.com/articles/25292>
15. Vogelstein B, Papadopoulos N, Velculescu VE, Zhou S, Diaz LA, Kinzler KW. Cancer genome landscapes. *science*. 2013 Mar 29;339(6127):1546-58. Available from: <https://science.sciencemag.org/content/339/6127/1546.abstract>
16. Maltoni CF, Holland JF. Chapter 16: Physical Carcinogens. Bast RC, Kufe DW, Pollock RE, et al. *Holland-Frei Cancer Medicine* (5th ed.). Hamilton, Ontario: BC Decker. 2000.
17. Peteros NP, Uy MM. Antioxidant and cytotoxic activities and phytochemical screening of four Philippine medicinal plants. *Journal of Medicinal Plants Research*. 2010 Mar 4;4(5):407-14. Available from: <https://academicjournals.org/journal/JMPR/article-abstract/6A2786415864>
18. Issa AY, Volate SR, Wargovich MJ. The role of phytochemicals in inhibition of cancer and inflammation: New directions and perspectives. *Journal of Food Composition and Analysis*. 2006 Aug 1;19(5):405-19. Available from: <https://www.sciencedirect.com/science/article/pii/S0889157506000196>
19. 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 Jan 1;2016. Available from: <https://www.hindawi.com/journals/omcl/2016/3685671/abs/>
20. Jain S, Hirst DG, O'sullivan JM. Gold nanoparticles as novel agents for cancer therapy. *The British journal of radiology*. 2012 Feb;85(1010):101-13. Available from: <https://www.birpublications.org/doi/abs/10.1259/bjr/59448833>
21. Gupta AK, Gupta M. Synthesis and surface engineering of iron oxide nanoparticles for biomedical applications. *biomaterials*. 2005 Jun 1;26(18):3995-4021. Available from: <https://www.sciencedirect.com/science/article/pii/S0142961204009317>
22. Grande F, Tucci P. Titanium dioxide nanoparticles: a risk for human health?. *Mini reviews in medicinal chemistry*. 2016 Jun 1;16(9):762-9. Available from: <https://www.ingentaconnect.com/contentone/ben/mrmc/2016/00000016/00000009/art00010>
23. Wason MS, Zhao J. Cerium oxide nanoparticles: potential applications for cancer and other diseases. *American journal of translational research*. 2013;5(2):126. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3612509/>
24. Sirelkhatim A, Mahmud S, Seeni A, Kaus NH, Ann LC, Bakhori SK, Hasan H, Mohamad D. Review on zinc oxide nanoparticles: antibacterial activity and toxicity mechanism. *Nano-micro letters*. 2015 Jul;7(3):219-42. Available from: <https://link.springer.com/article/10.1007/s40820-015-0040-x>
25. Mittal AK, Kumar S, Banerjee UC. Quercetin and gallic acid mediated synthesis of bimetallic (silver and selenium) nanoparticles and their antitumor and antimicrobial potential. *Journal of colloid and interface science*. 2014 Oct 1;431:194-9. Available from: <https://www.sciencedirect.com/science/article/pii/S0021979714004494>
26. Ahmad MZ, Akhter S, Jain GK, Rahman M, Pathan SA, Ahmad FJ, Khar RK. Metallic nanoparticles: technology overview & drug delivery applications in oncology. *Expert opinion on drug delivery*. 2010 Aug 1;7(8):927-42. Available from: <https://www.tandfonline.com/doi/abs/10.1517/17425247.2010.498473>
27. Kateb B, Chiu K, Black KL, Yamamoto V, Khalsa B, Ljubimova JY, Ding H, Patil R, Portilla-Arias JA, Modo M, Moore DF. Nanoplatfoms for constructing new approaches to cancer treatment, imaging, and drug delivery: what should be the policy?. *Neuroimage*. 2011 Jan 1;54:S106-24. Available from: <https://www.sciencedirect.com/science/article/pii/S1053811910001448>
28. Abdulwahab F, Henari FZ, Cassidy S, Winser K. Synthesis of Au, Ag, curcumin Au/Ag, and Au-Ag nanoparticles and their nonlinear refractive index properties. *Journal of Nanomaterials*. 2016 Sep 22;2016. Available from: <https://doi.org/10.1155/2016/5356404>

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