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Nanotechnology for Herbal Drugs and Plant Research.

Ankita Pandey[1], and Govind Pandey[2]*

[1]Department of Nanotechnology, Gyan Ganga College of Technology, Jabalpur, Madhya Pradesh, India.
[2]Department of Pharmacology and Toxicology, College of Veterinary Science & Animal Husbandry, Rewa (Nanaji Deshmukh Veterinary Science University, Jabalpur), Madhya Pradesh, India.

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*For Correspondence

Plot No. 3, Kanchan Parisar, Near Madan Mahal Railway Station, Wright Town, Jabalpur-482001, MP, India.
Mobile: +91 9713827709, 9893769290

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ABSTRACT

Nanotechnology is the new emerging technology in the drug discovery and it has the property of self targeting in the sense that without the attachment of a specific ligand, the nanoparticles can be used for targeting, due to their distinctively small size, at the infected pathological areas. Drug delivery system fetched a novel drug delivery system, a novel approach to overcome the drawbacks of the traditional drug delivery systems. Treatment of chronic diseases like cancer using targeted drug delivery nanoparticles is the latest achievement. By analyzing the relationship between nanotechnology and biological medicine, the application of nanotechnological methods for bioavailability enhancement of herbal drugs can be brought about. *'Bhasma'*, a natural product, is a metallo-medicine in powder form of nano to submicron size. At present, several nano drugs are under investigation for drug delivery and more specifically for cancer therapy. Interestingly, pharmaceutical sciences are using nanoparticles to reduce toxicity and side effects of drugs.

INTRODUCTION

The term *'nanotechnology'* was derived by Greek word *'nanos',* meaning *'dwarf'*. The nano device and nano strategy are one billionth of a meter or 10^{-9} m. The nanotechnology involves the clumps of atoms, molecules and molecular fragments into the extremely small particles between 1 and 100 nm, and puts forward to the interactions of molecular level matters and engineered materials characteristically. Nanotechnology is the new emerging technology in the drug discovery and it has the property of self targeting in the sense that without the attachment of a specific ligand, the nanoparticles can be used for targeting, due to their distinctively small size, at the infected pathological areas. Drug delivery system fetched a novel drug delivery system, a novel approach to overcome the drawbacks of the traditional drug delivery systems. Treatment of chronic diseases like cancer using targeted drug delivery nanoparticles is the latest achievement in the pharmaceutical drug delivery field [1].

Nanotechnology is an advanced scientific technique in the 21st century. By analyzing the relationship between nanotechnology and biological medicine, the application of nanotechnological methods for bioavailability enhancement of herbal drugs can be brought about. It is indicated that nanotechnology is one of the fastest developmental, the most potential and the far-reaching high and new technology in the present era, and it greatly promotes the development of biological medicine and bioavailability enhancement of herbal drugs. With the application of nanotechnology of nanomization of herbal drugs, it will make the development of nanoherbal drugs possessing high bioavaibility, which consequently will open the new era of herbal drug discovery [2]. The breakthrough in this regard will be achieved from the research of the nanomization of herbal drugs against cancer and various other diseases.

'Ayurveda' is the ancient Indian medical science based on herbs and herbo-mineral preparations. In Ayurveda, seven metals used therapeutically are: gold (Au), silver (Ag), copper (Cu), iron (Fe), lead (Pb), tin (Sn) and zinc (Zn). These are passed through many processes and finally transformed into therapeutic form. *'Bhasma'* is the metal based medicine prepared from metals after many systematic processes to raw metal into therapeutic form. *'Swarna bhasma'* (gold ash) is a therapeutic form of gold metal of nanosized particles when evaluated through various tools and techniques. The size of particle was found to be about 56 nm. Swarna bhasma was also analyzed

qualitatively and found that the final product is almost pure gold (Au). *'Bhasma'* is a metallo-medicine in powder form of nano to submicron size. The raw metal is converted into therapeutic form through classical process by repeated incineration and grinding with some herbal juices and other specified matters. Specialty of preparation process is that the whole process is not a chemical based, rather it is fully a mechanical process and chemical properties much differ to nanoparticles prepared through chemical process [3].

Use of nanotechnology in medicine and more specifically drug delivery is set to spread rapidly. Presently, many substances are under investigation for drug delivery and more specifically for cancer therapy. Interestingly, pharmaceutical sciences are using nanoparticles to reduce toxicity and side effects of drugs. From a positive view point, especially the potential to cross the blood brain barrier may open new ways for drug delivery into the brain. In addition, the nanosize also allows for access into the cell and various cellular compartments, including the nucleus. A multitude of substances are currently under investigation for the preparation of nanoparticles for drug delivery, varying from biological substances like albumin, gelatin and phospholipids for liposomes, and more substances of a chemical nature like various polymers and solid metal containing nanoparticles [4].

Herbal drugs have now occupied lead positions in the pharmacopoeia, and the improvement in this concern through nanoformulations using nanotechnology have been done. Known effects and no side effects have made natural products/herbal drugs a powerful therapeutic solution to the organisms. But the delivery of plant/herbal therapeutic molecules as drugs is problematic due to poor solubility, poor permeability, low bioavailability, instability in biological milieu and extensive first pass metabolism. These limitations of herbal drugs can be overcome by attaching or encapsulating them with suitable nanomaterials. The nanomaterials can significantly enhance the pharmacokinetics and therapeutic index of plant drugs. Targeted delivery and combination therapy can drastically improve the performance of herbal drugs [5].

Nanosized Herbal Drugs to Cure Cancer and Other Diseases

Herbal drugs/medicines (or herbal remedies) and natural products are being used since ancient times to cure various diseases. Unlike the existing the allopathic system, the herbal drugs have hundreds and thousands of constituents that all work together against diseases. The natural products produced by the organisms like fungi, bacteria, animals and plants act as biologically active agents. Mostly, the conventional pharmaceuticals or pharmacognostical products in the market are rooted from natural products and their derivatives with herbal products are playing pivotal role. All over the world, the research on such herbal remedies has been carried out in different areas, e.g., pharmacy, pharmacology and medicine. Incorporation of these herbal extracts into novel formulation systems is to be done in order to have advantages and to overcome their bulk dosing and less absorption which is the major problem being faced. Many of the significant natural products and their derived active components present in the market are: paclitaxol, doxorubicin (both anticancer drugs), lovastatin (anticholesterolemic), erythromycin, streptomycin, rafamycin (all antibiotics), cyclosporine-A and tacrolimus (both immunosuppressive), and amphotericin-B (fungicidal). Actually, in the context of conventional pharmaceuticals, these drugs have their existence from herbal remedies. Many drugs (e.g., asprin, salbutamol, digoxin, quinine, morphine, atropine, colchicine, bromelain, etc.) had been extracted from the plants as their active components for treating various diseases. Morphine was isolated as a first drug by Serturner from the plant opium popy (*Papaver somniferum*) as a pain killer. Quinine extracted from the cinchona tree (C*inchona officinalis*) is used to treat malaria, and aspirin isolated from willow bark is used for the treatment of fever. Most of the plants and formulations (e.g., Curcumin, Triphala, Pomegranate, Kalonji, Sariva, etc.) have explored the potential to cure cancer and inflammation [1].

The researchers have extracted the ingredients from Chinese plants to create a new drug to fight against cancer. By using nanotechnology, the research showed that the herbal drugs are able to enter cancer cells without damaging the healthy cells of the human body. The new drug was produced by extracting the cancer fighting ingredients of Chinese herbs like milkvetch root, saltwort, cassia twigs and liquorice root. The herbal drug nanotechnology reduced these ingredients to their smallest size, enabling them to enter cancerous cells without damaging healthy cells. It was also explained that the drugs first phase of animal testing has already been successfully completed with the patent rights in 42 countries. This new drug has four advantages: it only kills the cancerous cells; it has rapid medicinal effects; it does not harm other organs; and it can be ingested orally without a physician's supervision. When taken together with western medicine, the drug is also able to lower the dosage and reduce resistance to cancer drugs, thereby enhancing overall efficiency. During experiments, the herbal drug was reportedly found to be effective in alleviating symptoms of the cancers of lung, breast, bone, liver, tongue, cervix, ovary, brain and skin, and primary or metastatic lymphoma. The nano herbal drug was also reported to work well, especially against the lymphoma, where the tumour was to have softened, grown smaller in size or disappeared altogether after 2 months of treatment [3].

The highly stable micelles with the size of 10 to 40 nm can be prepared from poly (ethylene glycol)/phosphatidyl ethanolamine (PEG-PE) conjugates. These are easily soluble and can firmly retain substantial quantities of various poorly soluble anticancer drugs (m-porphyrin, tamoxifen, taxol). The stable drug-loaded

polymeric micelles may represent a convenient drug delivery system into tumours utilizing the enhanced permeability and retention effect [6]. Recent advances in drug delivery systems of camptothecin have improved this drug's efficiency in tumour due to development in nano-sized dosage forms of camptothecin-derived drugs. DNA topoisomerase is one of drug targets in cancer therapy. Camptothecin is a plant alkaloid derived from the Chinese tree *Camptotheca acuminate*. The alkaloid camptothecin caused DNA damage by specifically targeting DNA topoisomerase, effectively devastating a broad spectrum of tumours [7].

Nanotechnology has drafted plant viruses for drug delivery in cancer. The researchers have successfully modified a common plant virus to deliver drugs only to specific cells inside the human body, without affecting surrounding tissue. These tiny *"smart bombs"*- each one thousands of times smaller than the width of a human hair- could lead to more effective chemotherapy treatments with greatly reduced, or even eliminated, side effects. The researchers say that the virus is appealing in both its ability to survive outside of a plant host and its built-in "cargo space" of 17 nm, which can be used to carry chemotherapy drugs directly to tumour cells. The researchers deploy the virus by attaching small proteins, called *'signal peptides'*, to its exterior that cause the virus to 'seek out' particular cells, such as cancer cells. Those same signal peptides serve as 'passwords' that allow the virus to enter the cancer cell, where it releases its cargo. Out of different nanoparticles as cell-targeting vectors used, the plant virus is superior in terms of stability, ease of manufacture, ability to target cells and ability to carry therapeutic cargo. Calcium is the key to keeping the virus' cargo enclosed. When the virus is in the bloodstream, calcium is also abundant. Inside the individual cells, however, calcium levels are much lower, which allows the virus to open, delivering the cancer drugs only to the targeted cells. Another factor that makes the virus unique is the toughness of its shell. When the virus is in a closed state, nothing will leak out of the interior, and when it does open, it opens slowly, which means that the virus has time to enter the cell nucleus before deploying its cargo, which increases the drug's efficacy. The researchers believe that their method will alleviate the side effects of common chemotherapy treatments, while maximizing the effectiveness of the treatment. The nanoparticles can be stabilized and targeted to specific cells (such as cancer cells) by attachment of specific proteins to the nanoparticles. Viruses that lack a lipid envelope (i.e., they consist of a genome surrounded by a protein capsid and other protein structures) provide a molecularly precise container of known structure and organization to which targeting molecules can be attached. Encapsidation of various nanoparticles up to 17 nm in diameter by the 36 nm diameter *'Red Clover Necrotic Mosaic Virus' (RCNMV)* has been reported. This plant virus has a genome consisting of two single strand RNA molecules. The two genomic RNA molecules form a complex that binds the viral capsid protein and initiates the assembly of the virion. A small RNA molecule that mimics the site on the second genomic RNA required to initiate virion assembly can be tethered to various nanoparticles and then serve to initiate virion assembly, forming uniform virus-like particles about 33 nm in diameter- slightly smaller than the native virus particles- that encapsidate the nanoparticle within the protein shell. The relatively small size of the virus-like particles is an advantage because particles in the 30 nm range can be delivered directly to the cell nucleus via the nuclear pore complex. The virus-like particles are also sturdy enough to facilitate purification [8].

NANOTECHNOLOGY FOR PLANT RESEARCH

The researchers from Iowa State University have succeeded in using nanotechnology to insert and simultaneously activate genes delivered into the plant cell walls, a discovery that has powerful implications for biotechnology. While the process of delivering genes into plant tissue is not new, it has two stages. First, the gene is inserted into the plant cell tissue; and afterwards, the chemicals are introduced into the plant to trigger the genes function. The two-stage process has been imprecise as the presence of chemicals can be harmful to the plant. The new breakthrough solution uses what are called *'mesoporous nanoparticles'*. These nanoparticles both introduce the gene and activate it at the same time, in a precise and controlled manner without toxic effects. The scientists could potentially use this as an aid in imaging analysis of plants, which have been activated with the appropriate materials. The nanoparticles are chemically coated and act as containers for the genes that are delivered to the plants. The coating induces the herbal plants to swallow the particles, effectively ingesting them inside the plant cell walls where the genes could be inserted. The biologists have succeeded in using this technology to introduce DNA to tobacco and corn plants, among others. With nanotechnology, the researchers are able to impart several substances to the plants, all at once and release them in a time controlled manner. Being able to penetrate the cell wall of plant enables biologists to view the world of plant biology in all of its complex and intricate detail, opening vast new frontiers of discoveries for agriculture and other industries that rely on the biotechnology [3].

A laboratory study (at University of Delaware) has indicated that the plants can undertake the nanoparticles and accumulate these nanoparticles in their tissues. It shows that the nanoparticles can enter into human food chain. The major disadvantages with these nanoparticles are that the health risk associated with these particles has not yet been established. There are many concerns with the use of these nanoparticles, and even they can enter through breathing and can damage our vital organs. The researchers used low frequency monotone for vibrating the dried pumpkin plant and unique magnetic signals were able to reveal the location of nanoparticles inside the plants. The investigators further carried out the research on pumpkin grown in sand and soil, and found that there is little and no uptake of nanoparticles in comparison to the strong uptake in pumpkin plants grown in aqueous solution. The investigators (at Texas Agri Life Research) are planning to use nanotechnology for detecting

plant diseases at an early stage, so that tons of food is protected from the possible outbreak. Presently, the detection technique takes days to find plant diseases, but now the researchers are focusing to find a short detection system that can give results within a few hours. For achieving this goal, the plant pathologists are joining hands to the nanotechnology specialists, so that the combined efforts could lead to a better detection system. The researchers are looking for a simple system that is portable and accurate, and does not require any complicated technique for operation, so that even a simple farmer can use the portable system and can address the diseases [3].

CONCLUSION

Nanotechnology has the property of self targeting in the sense that without the attachment of a specific ligand, the nanoparticles can be used for targeting, due to their distinctively small size, at the infected pathological areas. Treatment of chronic diseases like cancer using targeted drug delivery nanoparticles is the latest achievement of nanotechnology. By analyzing the relationship between nanotechnology and biological medicine, the application of nanotechnological methods for bioavailability enhancement of herbal drugs can be brought about. With the application of nanotechnology of nanomization of herbal drugs, it will make the development of nanoherbal drugs possessing high bioavaibility, which consequently will open the new era of herbal drug discovery. At present, several nano drugs are under investigation for drug delivery and more specifically for cancer therapy.

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