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Nanopharmaceutics and Pharmacognosy Integration for Targeted Delivery of Bioactive Compounds from Medicinal Plant Sources

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Abstract

Nanopharmacy and Pharmacy are both relatively new fields of study focused on utilizing plant-sourced bioactive metabolites to produce medicines with greater effectiveness. Numerous phytochemicals possess powerful biological activity; however, very few are actually used in clinical practice due in part to their poor solubility, low bioavailability, limited stability, and rapid clearance or metabolism. The combined efforts of Nanopharmacy and Pharmacy have created new methodologies for the effective and accurate delivery of natural products by employing various forms of nanocarriers. Among other benefits, Nanocarriers enhance phytoconstituents' stability, enhance the extent of their absorption, and provide for target-specific delivery while minimizing phytoconstituents' toxicity and adverse effects. The multidisciplinary collaboration of Nanopharmacy and Pharmacy has the potential to reduce the required dosage and maximize the duration of pharmaceutical products—the result being an increase in the effective therapeutic benefits of natural products. Additionally, advanced forms of nanoformulations improve the permeability of biological barriers and enhance the cellular bioavailability of herbal bioactives. Green methods of synthesizing nanopharmaceuticals from plants provide increased safety and environmental stability in

the development of nanomedicines. The combined efforts of Nanopharmacy and Pharmacy provide an exciting opportunity to develop safe, effective, and targeted herbal medicines for use in present day medical systems, as well as inspire future pharmaceutical innovations.

INTRODUCTION

Throughout history, traditional and modern health care have relied heavily on plants as sources of medicine. The active ingredients found in nature (e.g., flavonoids, terpenes, phenolics and alkaloids) have a variety of benefits. Some common benefits include: being antioxidant, anti-inflammatory, and anticancer agents; acting as antibiotics; and helping prevent age related diseases. The amount of medicine that is currently available from plants is limited by several factors, such as being poorly soluble in water, not getting absorbed into the body (due to having low bioavailability), rapidly degrading once ingested, or being limited to a specific target in the body (i.e. only working on a certain part of the body). These limitations on the use of plant-derived medications in the clinic have led to a demand for better drug delivery systems. Recently, interest in pharmacognosy has been growing due to increased demand for more natural and safer ways to treat illness. By incorporating traditional knowledge about the use of plants in healing with modern technology (i.e. improving medications by making them easier to deliver), researchers are finding new ways to improve how herbal medicines work; specifically, researchers are investigating various technologies that can help overcome physical, chemical and biological barriers associated with the active ingredients in plants. As such, using nanotechnology to enhance the effectiveness of natural active ingredients from plants and help develop new forms of herbal medicine has become of great interest to both the scientific and medical communities. (Patra et al., 2018)

Nanopharmaceutics involves using nanotechnology within the field of pharmaceuticals to improve drug delivery, how well drugs work, and how safe a drug is. Various types of nanocarriers are available, including liposomes, polymer nanoparticles, nanoemulsions, dendrimers, solid lipid nanoparticles, and metallic nanoparticles. These types of delivery systems have the capability to effectively deliver bioactive compounds to target tissues/cells. Using nano-sized delivery systems can improve the stability and solubility of phytochemicals while protecting them from being broken down by enzymes and undergoing premature metabolism. In addition, nanopharmaceutical systems allow for controlled/repeated release of a drug and can reduce how often a person needs to take a particular medication and limit potential side effects. As a result of their very small size, nanoparticles have an easier time being absorbed by the body and penetrating biological membranes, which results in better uptake by cells and a more effective

therapeutic response. Research in herbal medicine has shown that nanoformulations significantly increase the effectiveness of compounds such as curcumin, quercetin, resveratrol, and berberine. Therefore, it is believed that nanoformulation of poorly bioavailable plant components could be converted into clinically valuable therapeutic agents for the treatment of many diseases, including cancer, diabetes, and infectious diseases.(Yadav et al., 2020)

Pharmacognosy is critical to locating, extracting, isolating, and characterizing the bioactive ingredients derived from medicinal plants. Advances in phytochemical analysis and biotechnology facilitate the identification of many plant-based compounds with medicinal properties. However, successful clinical application of these compounds is primarily determined by the efficient delivery of the active ingredient to the intended site of action. Traditional herbal medicine has limitations due to variable absorption rates and unreliable pharmacokinetics resulting in reduced therapeutic efficacy. The integration of nanotechnology with pharmacognosy provides a solution to the challenges posed by these limitations through enhancement of the physicochemical characteristics of plant-derived compounds. Nanocarriers can encapsulate vulnerable plant-derived ingredients and allow for drug targeting to a specific anatomical location, thereby maximising therapeutic effect while minimising deleterious effects on surrounding healthy tissue. Use of biodegradable and biocompatible materials within nanocarriers will also facilitate safer drug application. These advances also have led to the creation of new dosage forms (i.e., nanosuspensions, phytosomes, nanogels) that enhance patient compliance and therapeutic efficacy. Therefore, collaboration between the discipline of pharmacognosy and the discipline of nanopharmaceutics continues to be among the most exciting and rapidly evolving areas of pharmaceutical research and development. (Mukherjee et al., 2019)

Integrating nanopharmaceutics and medicinal plant research has a major benefit to targeted drug delivery. Traditional methods of drug delivery distribute the active ingredient throughout the entire body which results in decreased efficacy and increased side effects. In comparison, nanoparticles can provide targeted delivery of the bioactive ingredients to areas of disease (disease tissue) so there is higher precision in therapy and less system toxicity. The modification to the surface of the nanoparticles using a variety of ligands, antibodies, or polymeric materials can also assist in the targeted delivery and the interaction at the specific receptor level. This process of delivering anticancer agents derived from plants directly to cancer cells while minimizing the exposure of healthy tissue makes a significant contribution to the advancement of cancer care. Another significant advantage of utilizing nanoformulations is that they can

cross complex biological barriers, such as the blood-brain barrier, which allows for effective treatment of neurological disorders with compounds derived from plants. The other advantage of employing green synthesis methods for the preparation of nanoparticles with plant extracts represents a more sustainable and economically viable process of producing nanomedicine products. Thus, nanodrug delivery has the potential to reshape the landscape of herbal medicine and offer improved therapeutic approaches to the modern healthcare system. (Khan et al., 2021)

The convergence of pharmacognosy and nanopharmaceutics shows promise for developing new medicines derived from nature and facilitating the evolution of personalized therapeutics. Advancements in molecular biology, phytochemistry, and nanotechnology will result in highly advanced herbal nanoformulations with improved therapeutic outcomes. Researchers are working on optimizing various parameters such as nanoparticle size, surface properties, encapsulation efficiencies, and release kinetics to provide the most benefit for patients. There has also been a growing recognition among regulatory bodies and the pharmaceutical industry of the need for standardized herbal nanomedicines to ensure safety and efficacy. While there have been commitments to progress in these areas, challenges remain regarding large-scale production, toxicity assessment, quality assurance, and regulatory acceptance that require continuing support. There will need to be greater emphasis put on clinical trial processes, long-term safety studies, and sustainable manufacturing methods to bring plant-based nanomedicines to market successfully. The partnership between pharmacognosy and nanopharmaceutics ultimately represents a strong scientific basis from which to create novel targeted delivery systems that will both increase the therapeutic benefits of medicinal plants' bioactive compounds and significantly impact the advancement of global healthcare. (Ahmed et al., 2022)

Nanopharmaceutics improves herbal drug delivery

The field of Nanopharmaceutics has totally changed the way we deliver herbal or plant-sourced therapy items such as medicine by improving the delivery method for use in delivering those substances into the body. While herbal products contain many beneficial properties through their use, the lack of absorption rate, lack of stability, and the ease of breaking down in human bodies greatly limit the effectiveness of those products in getting their intended result and limit the number of cases in which they can be prescribed for off-label use or for medical use. One method of overcoming this limitation of herbal medicines is through the use of Nano-Size Delivery Vehicles that

improve the physicochemical properties associated with delivering herbaceous compounds through the body. Herbal products are better suited for delivery to their target tissue with this method; therefore, they may achieve greater bioavailability and have improved therapeutic benefits when using them as stated above. There is a growing interest from researchers in the area of combining traditional herbal medicine with modern, advanced pharmaceutical technologies for the research and development of natural medicines. Nanopharmaceutics assists in developing a modern method of dispensing or performing the function associated with using herbal medicine products. (Singh et al., 2017)

The use of nanopharmaceutics for delivery of herbal drugs has many benefits including: Increased solubility and dissolving rate of poorly water-soluble herbal active ingredients (phytochemicals) is one major benefit of using nanopharmacutics to deliver herbal medicines; Many active components derived from herbs or medicinal plants (like curcumin from turmeric, silymarin from milk thistle, catechins from green tea) have such poor solubility in water that they cannot dissolve and therefore be absorbed after being taken by mouth; Formulations of nanomaterials like nanosuspensions, solid lipid nanoparticles and nano emulsions enhance the surface area of and dispersion of these active ingredients to increase their solubility in solution as well as their ability to be absorbed into the bloodstream after dissolving in the gastrointestinal (GI) tract; With an increase in solubility of the herbal active ingredient(s) there will be an increase in the amount of active ingredient(s) circulating throughout the body and thus increasing the efficacy of the herb; Additionally, nanotransport mechanisms provide stability for the active ingredients contained within by protecting the active ingredients against oxidation, hydrolysis and enzymatic degradation; Prolonging the shelf-life of the active ingredients by preserving their integrity will result in more consistent therapeutic action of the herbs; Consequently, nanopharmaceutical systems are essential for maximizing the potential of herbal medicine through overcoming the obstacles associated with using traditional herbal medicines. (Rai et al., 2018)

A major advantage of using nanopharmaceutics for delivering herbal medicines is the targeted delivery of their active ingredients. Herbal remedies are typically given in an indiscriminate manner, leading to low efficacy and significant side effects. Nanocarriers can be created that specifically deliver the bioactive ingredients of a particular botanical to areas of disease by using both passive and active targeting systems. By modifying the surface characteristics of the nanoparticles with ligands, antibodies, or polymers, their

ability to recognize and bind to specific receptors on the target cell is maximized. A targeted delivery system allows for greater concentrations of bioactive compounds from botanicals to be delivered to where they are needed while limiting toxic effects on healthy tissue. Targeted delivery is especially useful in the treatment of cancer; plant-based compounds have been shown to effectively inhibit the growth of tumors while having few systemic side effects. Additionally, nanoparticle systems can provide controlled and sustained releases of herbal drugs, so the number of doses needed to be taken can be reduced, and patient compliance can be increased. Ultimately, nanopharmaceutics has improved herbal drug delivery into a more accurate, efficient and patient friendly method of treatment. (Gupta &Vyas, 2019)

Nanopharmaceutics also improve herbal bioactive compound permeability/cell uptake since the bioavailability of these compounds is hindered by biological barriers such as intestinal membranes, blood-brain barriers, etc., hence there is a greater chance for nanoparticles (size/shape) to cross over these barriers compared to standard dosage forms. Thus, by providing improved penetration, nanoparticles result in greater intracellular accumulation and enhancement of the pharmacological effect of these compounds. This is especially important in treating neurological disorders and in treating infections inside the cells, where effective drug transport is much harder to achieve. Lipid-based and polymeric nanoparticles have also been very successful at improving the delivery of herbal compounds to brain tissue/infected cells. Furthermore, nano-based delivery systems help to slow down the rapid removal of phytochemicals from the blood, thus enhancing their therapeutic effect. Therefore, the ability of nanoparticles to improve absorption and penetration into tissues will be critical in further developing modern herbal medicine and targeted therapy. (Chauhan et al., 2020)

The development of future herbal remedies is heavily reliant on advances made within the field of “nanopharmaceutics,” as it applies to the delivery systems that transmit these products to patients. There is a growing emphasis within this area by researchers toward developing nanoparticles from naturally occurring (plant based) materials and utilizing green synthesis methods, which are viewed as environmentally friendly. Additionally, the use of these sustainable methods reduces potential hazards associated with the direct use of chemicals in the development of nanomedicine. Evidence of this is evident through the progress made by developing safer, biodegradable, etc., nanoparticles; however, many obstacles still exist that prevent large-scale manufacturing such as continuing to develop valid quality control standards (e.g., quality control for

herbal medicine), have proper toxicity testing, and determining whether or not products should receive regulatory approvals. In light of these challenges, it will continue to be critical to conduct extensive clinical trials followed by clearly defined manufacturing protocols in order to demonstrate both the quality and safety of nanoformed herbal remedy products. On a positive note, nanopharmaceutics provide countless opportunities to enhance the efficacy of plants used as medicine and allow for expanded use of herbal remedies in modern medicine. Additionally, nanotechnology provides useful tools for overcoming the limitations (e.g., inefficiency) of traditional herbal medicines by offering new innovative methods of developing high-quality, natural based medicines that are able to address global health challenges and enhance overall patient outcomes. (Sharma et al., 2021)

Pharmacognosy studies medicinal plant compounds

Pharmacognosy is a specialized area within the field of pharmacy that studies all of the different ways that medicine can be made from plants and other things that can be found in nature. For thousands of years, plants have been one of the most important sources of the medicine used in many traditional systems of healing, such as Ayurveda, Unani, and Traditional Chinese Medicine. Pharmacognosy includes ways to identify, collect, grow, extract, and test any substances in plants, microorganisms, and all sources from the ocean that are used to make herbal medicines. There are a variety of different kinds of chemicals found in medicinal plants known as phytochemicals, such as Alkaloids, Flavonoids, Tannins, Glycosides, Terpenoids, and Phenolic Compounds; all of these chemicals have a range of biological activities that can be beneficial to human health. When looking at the five most common types of phytochemicals: Antimicrobial, Antioxidant, Anti-inflammatory, Anticancer, and Antidiabetic; it is easy to see how any of these types of plants can play a critical role in preventing or treating disease. Because there is such an increase worldwide for natural medicines, pharmacognosy has become one of the most important branches of modern healthcare and pharmaceutical research. There are ongoing studies focused on studying plants that have previously been used for medicinal purposes to help find new products that can provide the same or similar therapeutic effects without the side effects found with many manufactured pharmaceuticals. Ultimately, pharmacognosy is extremely important for helping connect traditional herbal medicine knowledge with the latest scientific research and innovation in developing new medicines. (Balunas&Kinghorn, 2017)

To initiate the process of studying medicinal plant components in pharmacognosy, proper identification and classification of plant materials must be performed. Accurate authentication of medicinal plant materials is crucial to guarantee the quality, purity, and safety of herbal products. Morphological, microscopic, and phytochemical analyses are commonly performed for the determination of species, as well as to evaluate if the materials have been adulterated or contaminated. In addition to identifying plant materials, researchers study geographic distributions, cultivation methods, and harvesting practices pertaining to plants that influence the concentration of active (meaning bioactive constituents) in the plants. Environmental conditions that impact phytochemical production include climate, soil type, and seasonal changes. After being properly identified, plant materials are typically extracted and isolated to obtain pure forms of bioactive substances for further evaluation from pharmacologic standpoints. Due to advances in technology (i.e., chromatography & spectroscopy) in analyzing certain components, the efficiency of research into phytochemicals and identifying natural products has improved. These advancements in science have allowed pharmacognostists to play an increasingly important role in the standardization and quality control of herbal medicines used throughout the world. (Evans, 2018)

The field of pharmacognosy also serves an important role in discovering new medications based on natural sources for treating illness. The majority of traditionally used chemically-derived drugs can trace their origins back to plant-derived sources that have been discovered by pharmacognosy. Some examples of drugs that are used today that were developed from plants include quinine, which was obtained from Cinchona bark and used to treat malaria; morphine, which was derived from Papaversomniferum and used for pain relief; and paclitaxel, which came from the Taxus species of trees and is used to treat cancer. These drug developments illustrate the tremendous potential of medicinal plants for use in the pharmaceutical sciences. Continued research is currently being conducted by scientists on previously untested species of plants to discover new naturally occurring chemical compounds with therapeutic properties that are indicative of future use against both chronic and infectious diseases. Bioassay-guided fractionation techniques methodically isolate the biologically active constituents that produce therapeutic results while looking for naturally occurring chemical compounds unique to each plant. Recent advancements in biotechnology and molecular pharmacognosy have provided scientists with a greater understanding of how certain herbal compounds exert their effects at the cell and molecular levels. This information provides greater credence to the use of herbal medicines and has been critical to providing support to the

development of new and safer pharmaceutical products based on plants for modern health care use. (Cragg& Newman, 2019)

Pharmacognosy has broadened in scope in recent years as new technology has been introduced to medicine; namely biotechnology, nanotechnology and pharmacophysics. As a result, scientists and researchers are creating new ways to improve how we deliver plant-derived compounds from nature's pharmacy into humans as therapies. Unfortunately, there are many limitations when using phytochemicals such as; limited solubility, low bioavailability and very metabolism which renders them ineffective in treating illness for patients. In addition, in recent years several new delivery systems which are using technologies (e.g. nanoparticles, liposomes, etc.) have been developed for the successful targeted delivery of herbal bioactives. The pharmacognostic sciences also support the development of nutraceuticals, cosmeceuticals and functional foods from plants that have medicinal value. In addition, the sustainable conservation and harvesting of our medicinal plants has gained importance as a way to protect biodiversity and to ensure the continued protection of our ecological balance and a source of invaluable plant sources for the use of future generations. Therefore, pharmacognosy will continue to adapt to the ever-changing dynamics of this scientific discipline through the integration of traditional knowledge with modern/advanced pharmaceutical technologies. (Sasidharan et al., 2020)

The outlook for pharmacognosy is bright, mainly because there is so much global interest in natural products and herbal therapies. Scientific validation of medicinal plants through pharmacological and clinical studies has enhanced public confidence in the use of herbal medicine. Researchers are now focusing on locating new natural products that are useful for treating emerging diseases and for combating drug-resistant pathogens. The advancements in genomic research, metabolomics, and artificial intelligence will continue to advance research on natural products and accelerate the process of discovering new drugs. Although there are issues associated with the standardization, quality control, and clinical evidence of herbal medicines, they are being addressed by regulatory agencies and health organizations that are advocating for the proper evaluation of herbal medicines with respect to their safety and effectiveness. Collaboration between traditional healers, researchers, and pharmaceutical companies will aid in the development of innovative therapies derived from plants as well as promote the continued establishment of sustainable healthcare practices. Overall, pharmacognosy has been, and will continue to be, an integral discipline within

pharmaceutical sciences that plays a significant role in helping identify, develop, and promote the many therapeutic uses of plant-derived medicines for improving human health. (Petrovska, 2021)

Nanocarriers increase bioavailability and stability

Nanocarriers are vital in contemporary pharmaceutical science, primarily because they enhance the bioavailability of therapeutic agents, including plant-derived bioactive compounds, through improved stability. A number of herbal compounds are known to have potent pharmacological effects, yet many are poorly soluble in water, have low permeability through biological membranes, and are quickly degraded while in the body. As a result of these limitations, poorly soluble drugs are less likely to be absorbed and not as effective when administered using conventional dosage forms. Nanocarriers are specifically engineered at the nanoscale to encapsulate bioactive compounds within a structural framework, thereby facilitating their targeted delivery and use at the intended site of action. The common types of nanocarrier systems used in the field of nanomedicine include: liposomes, polymeric nanoparticles, solid lipid nanoparticles, nanocapsules, dendrimers and nanoemulsions. Nanocarriers enable the dissolution and absorption of poorly soluble phytochemicals from the gastrointestinal tract by providing a nanoscale particle size and a high surface area. Additionally, nanocarriers protect bioactive compounds from oxidative, hydrolytic and enzymatic degradation during circulation through the body. For these reasons, formulations that utilize nanocarrier systems are significantly more effective at delivering therapeutic effects from herbal products, and will therefore drive further advancements in the application of targeted drug delivery systems in modern medicine.(Mishra et al., 2018)

Nanocarriers serve a key role in enhancing the bioavailability of poorly soluble therapeutic agents. Bioavailability is the amount of a drug that enters the systemic circulation and is therefore available for therapeutic action. Some compounds derived from plants like curcumin, quercetin and resveratrol have limited bioavailability when administered orally due to their poor water solubility and rapid metabolism. By decreasing the particle size and increasing the surface area of these compounds in contact with biological membranes, nanocarriers enhance the solubility and dispersibility of these compounds. This increased solubility and dispersibility will promote faster dissolution and improved absorption through the intestinal wall. Lipid-based nanocarriers are particularly effective in promoting transport via the lymphatic

system and in reducing first-pass metabolic effects in the liver, thereby enhancing the systemic bioavailability of herbal sources. The controllable release characteristics of nanocarriers will also provide for sustained drug concentration in the blood stream for longer periods of times; this will result in optimally improved therapeutic outcomes and minimally effective doses of the drug. Thus, the use of nanocarrier systems represents an invaluable tool for the optimization of the medicinal properties of natural products and improvement in the therapeutic response of patients receiving treatment. (Kumari et al., 2019)

Nanocarriers help to enhance bioactive compounds' chemical and physical stability. Many phytochemical compounds are vulnerable to different types of environmental conditions, including humidity, heat, light, and oxygen. This can degrade the active materials in those compounds and cause them to lose their effectiveness/therapeutic potential. Encapsulating the active ingredients inside a nanocarrier provides a protective barrier against these environmental stresses and will keep the ingredient from degrading before they reach the pharmacy or become unstable in storage prior to their administration, thereby extending the shelf life of the pharmaceutical formulation and providing consistent drug delivery performance. Polymeric nanoparticles and liposomes are the two most commonly utilized systems to stabilize unstable compounds and increase their biological activity for an extended period. Additionally, nanocarriers reduce drug interactions with non-target cells, tissues, and enzyme sources that would inactivate drugs prior to their reaching the intended destination. The increased stability afforded by the use of nanocarriers will produce more reliable formulations and facilitate the production of effective herbal medicines to be marketed commercially as pharmaceuticals. In summary, nanotechnology has significantly enhanced the long-term storage and delivery of sensitive quick-acting medicinal compounds. (Patel &Agrawal, 2020)

Nanocarriers have another significant benefit in improving targeted delivery of therapeutic agents and enhancing their cellular uptake. In general, conventional dosage forms distribute medication throughout the body nonselectively, leading to decreased efficacy and increased adverse reactions. With their ability to be engineered with surface modifications to identify certain tissues or receptors, nanocarriers provide site-specific delivery of medications. Nanocarriers also have a nano-scale size that allows them to penetrate biological barriers more easily, such as cellular membranes and the blood-brain barrier. Because of their increased cellular uptake, nanocarriers can deliver a

greater concentration of drug to the cell and improve pharmacological effects when treating conditions such as cancer and neurological disorders. Some nanocarriers are also designed to respond to various environmental stimuli (i.e., pH, temperature, or enzymes) causing them to release the drug in a controlled manner at the desired site. As a result of these advanced delivery properties, nanocarriers can significantly improve the accuracy of treatment while reducing the overall toxicity. Therefore, nanocarrier-based drug delivery systems are receiving increased attention within the pharmaceutical industry and in developing personalized medicine (Verma et al., 2021)

There is a lot of excitement about using nanocarriers in pharmaceutical and herbal medicine in the future because of the ongoing research and advances in both nanotechnology and biomedical research. Many researchers are developing new biodegradable, biocompatible and environmentally-friendly nanocarrier systems to enhance patient safety and to minimize environmental impact. Green synthesis methods that utilize natural polymers and plant-derived materials are gaining interest for developing sustainable nanomedicines. In spite of these many benefits, there is still a lot of work to be done to address some of the identified challenges associated with the use of nanocarriers, including toxicity issues, large-scale production issues, regulatory approval issues and long-term safety assessment issues. Continued research in clinical trials, and the continual development of new pharmaceutical products will likely create an environment conducive to the continued acceptance and commercialization of nanocarriers on a global basis. Future research will likely explore the potential to develop multifunctional nanocarriers that can simultaneously diagnose and treat, or theranosticnanocarrier systems. Thus, nanocarrier technology represents a significant improvement in bioavailability, stability and therapeutic effectiveness for medicinal compounds and contributes to improved healthcare and the delivery of novel treatment options in the future. (Raza et al., 2022)

Targeted delivery reduces side effects

One of the most significant technological advancements in pharmaceutical research is targeted drug delivery because of its ability to enhance the efficacy of treatments with less adverse reactions. Traditional drug delivery methods distribute the drug(s) throughout the patient's body in an uncontrolled manner, exposing non-diseased (healthy) tissues to therapeutic agents and causing side effects. This is particularly troubling when treating patients who have been treated with anticancer, antimicrobial,

and anti-inflammatory medications, all of which have the potential to cause significant morbidity due to their inherent toxicity. Targeted delivery systems are specifically designed to deliver the drug(s) directly into diseased tissues and/or cells while minimizing exposure to normal organs. The role that nanotechnology plays in the development of these advanced drug delivery systems, which utilize nanoparticles, liposomes, micelles (or similar), and/or polymeric carriers, has made it possible for pharmaceuticals to have increased precision during delivery and decreased unwanted systemic distribution. The increased efficiency of targeted drug delivery results in better overall treatment outcomes, lower levels of toxicity to patients, and a higher level of patient compliance. As such, researchers are increasingly focusing their attention on the development of targeted drug delivery systems to enhance both synthetic and herbal medicines. (Allen &Cullis, 2017)

Targeted delivery leads to reduced side effects, in part, by controlling the systemic distribution of therapeutic agents throughout the body. Conventional medicine routes the drug(s) through the blood stream before arriving at the disease site. During this entire process, the target organ may be exposed to the drug, thus exposing the body to the potential of adverse effects such as organ toxicity, gastrointestinal upset, and immune suppression. Targeted delivery systems utilize carriers that will preferentially accumulate in the diseased tissue through a mechanism of either passive or active targeting. Passive targeting uses the enhanced permeability and retention (EPR) effect, which is observed on many tumor tissues, to achieve the preferential accumulation of the drug. Conversely, in active targeting, the carrier is modified at the surface with different ligands, antibodies, or peptides that can recognize specific receptors on the surface of the target cells. By achieving either method of targeting, drug exposure to the healthy organs is reduced, while the localization of the drug at the treatment site is improved. By achieving restricted localization of the drug, targeted drug delivery systems allow lower doses of drug(s) to be administered to achieve the desired therapeutic response than would otherwise be required with conventional drug delivery systems. Thus, by targeting drug delivery, both improved patient safety and more effective treatments for disease and pharmaceutical drug therapy can be achieved.(Torchilin, 2018)

A major advantage of targeted delivery systems is that they allow for controlled and sustained release of therapeutic compounds to patients. The traditional dosage forms tend to release their medication immediately after ingestion--this results in large

amounts of the medicine being in the body at one time, ultimately resulting in toxicological consequences or other negative effects from taking too much medicine at once. However, the systems used with targeted delivery are specifically designed to allow for a gradual release of therapeutic compounds over an extended period of time, and as such, allow the blood concentration of the therapeutic agent to remain stable. When using a system that allows for controlled release, fluctuations in blood concentration will be minimized, and therefore the chances of experiencing side effects due to dosage will also be reduced. There are several types of delivery systems that can provide controlled and sustained release of drugs (i.e., polymeric nanoparticle formulations, hydrogels or liposome formulations). Additionally, due to the fact that the aforementioned systems have a greater number of dosing days, the patient will experience less discomfort than with conventional dosing, therefore increasing the likelihood of them complying with treatment regimens. Lastly, because of how advanced targeted delivery systems are, they will also respond to changes in pH, temperature, or enzyme activity in the environment, thus providing more accurate timing of when medications will be released from the targeted delivery system and be absorbed by the patient at the affected site. Therefore, this advance in drug delivery systems plays a significant role in minimizing systemic toxicity and, as a whole, improving the safety of drugs that will be used for chronic or severe diseases. (Khan et al., 2019)

The role of targeted delivery systems (TDS) in cancer therapy is significant, as traditional chemotherapy can damage normal cells as well as cancerous cells. This can lead to undesirable side effects, including hair loss, nausea, fatigue, and suppression of the immune system. Nanocarrier-based (NCB) targeted therapies enhance the ability to deliver anticancer drugs selectively to the site of the tumor tissue, while at the same time reducing their exposure to surrounding unaffected normal cells. Examples of nanocarriers used to deliver anticancer drugs include liposomes, dendrimers and antibody-conjugated nanoparticles. TDS can improve the intracellular uptake of drugs, thereby increasing their effectiveness against resistant cancer cell lines. Beyond oncology, the TDS technology presents a hopeful prospect for treating neurological disorders, cardiovascular disease and infectious diseases. For example, drug carriers capable of crossing biological barriers (e.g., the blood-brain barrier) permit effective treatments for conditions within the brain, while minimizing any harmful effects from these drug carriers on non-targeted tissues. Therefore, targeted delivery systems provide an enormous advance in creating safer and more personalized/matched therapeutic options in modern-day medicine.(Bae& Park, 2020)

As a result of the rapid advancements that have occurred in nanotechnology, biotechnology, and pharmaceutical engineering, the field of targeted drug delivery has a very bright future. Researchers are currently working on the development of multifunctional delivery systems that will allow for the ability to perform a patient's diagnosis, monitor the patient's condition, and treat the patient all at the same time. New design strategies for the development of biodegradable and biocompatible carriers will allow for the minimisation of long-term toxicity and environmental impact associated with target drugs. However, the continued existence of several unresolved issues related to target drug delivery, including high manufacturing costs, regulatory approval, formulation stability, and long-term safety evaluation of targeted drugs must be addressed. Therefore, there is a need to conduct adequate clinical trials to establish the safety and effectiveness of targeted drug delivery systems before they can be commercialised. However, technological and scientific advancements and continued research are anticipated to surpass these barriers and allow for advancements in the accuracy of therapeutic targeting. Targeted drug delivery is changing the way patients are treated by giving patients safer therapies with lower side effects, as well as fostering better outcomes. This novel methodology has the potential to change the course of medicine and general, as well as, increase the quality of life for patients with chronic and/or terminal illnesses. (Lammers et al., 2021)

Nanoformulations enhance therapeutic efficacy

Nanoformulations are academically gaining good attention, as they are reported to increase the therapeutic efficacy of the drugs and bioactive compounds. Many conventional medicines and plant-derived phytochemicals are unable to reach therapeutic concentrations because of their low solubility, low bioavailability, rapid metabolism, and poor target specificity. Nanoformulations are essentially designed nanoscale drug delivery systems aimed at enhancing the physicochemical and biological properties of the therapeutic agents. such systems consist of nanoparticles, nanoemulsions, liposomes, nanogels, dendrimers, and solid lipid nanoparticles. Owing to their smaller particle sizes, enhanced surface area, nanoformulations generally exert better dissolution, absorption, and penetration through biological membranes. They protect active ingredients from degradation and early elimination from the body, thus increasing the concentration of medications at the site of action and, consequently, increasing efficacy. Merging nanotechnology with pharmaceutical sciences thus has indeed become an avenue toward an encouraging approach to enhancing performance

traits of both, synthetic and herbal medicines, in modern healthcare. (Sahoo&Labhasetwar, 2017)

Nanoformulations provide numerous advantages, including the improved bioavailability of drugs that are unable to dissolve well in biological fluids due to their poor solubility. Many therapeutic compounds do not generate adequate clinical effects due to not efficiently dissolving in biological fluids or not being able to pass absorption barriers. The increased surface area of nano-sized formulations in contact with biological tissue leads to an increased dissolution rate of the drug and allows it to be absorbed more quickly into the systemic circulation. nanoemulsions, solid lipid nanoparticles (SLNs), and other lipid-based nanoformulations are very successful at enhancing the oral delivery of hydrophobic drugs due to their increased bioavailability. In addition, greater amounts of the drug that is administered can reach its target site due to the increased bioavailability, thus resulting in improved pharmacological activity and reduced need for higher doses. Lower doses of drug can also lead to fewer adverse events and improved safety for the patient. Additionally, nanoformulations can provide longer circulation times within the bloodstream, thus providing longer therapeutic effects in the body. Consequently, the increased bioavailability of drugs from nanoformulations is a significant contributor to the overall improvement in therapeutic efficacy associated with nanoformulation technology. (Müller et al., 2018)

Nanoformulations also significantly improve therapeutic efficacy by providing targeted and controlled drug release. Conventional drug delivery methods often result in rapid and random release of drugs around the body resulting in low therapeutic efficacy and unwanted side effects. Nanoformulations can be specifically engineered to actively or passively target diseased cells or tissue using a combination of passive and active targeting mechanisms. Surface modification with specific ligands, antibodies, or polymers enhance the interaction of nanocarriers with target cells allowing for precise localization of the drug at the site of action. The controlled release characteristics of nanoformulations maintain stable drug concentrations at the site of action, reducing the potential for toxicity due to rapid fluctuations in drug concentration at the site of action. These characteristics are especially beneficial in treating cancer using anticancer therapies as the targeted delivery of these drugs reduces collateral damage to adjacent healthy tissue while providing therapeutic benefit to the tumor. In addition, responsive nanoformulations can provide controlled drug release based on trigger conditions such as changes in temperature or pH. Seeking to exploit these advanced delivery systems

will improve the accuracy of treatment by reducing the potential for unwanted side effects and improving patient compliance. (Patel et al., 2019)

Another key factor contributing to improving therapeutic efficacy with nanoformulations is improved cell uptake and penetration of biological barriers. An important limitation to the delivery of therapeutic agents to their site of action is the limit caused by various biological membranes (the intestinal barrier, the blood-brain barrier, cellular membranes, etc.). Nanoformulations have physical and chemical characteristics that allow them to penetrate these barriers easily and, therefore, increase the amount of drug that accumulates inside the cell. The increased internalization of drugs into cells improves the interaction of the drug (therapeutic agent) to its target generated and provides a greater pharmacological response. With respect to neurological diseases, the use of nanoformulations allows for effective delivery of drugs across this barrier, which many traditional formulations can't accomplish. Nanoformulations also improve the efficacy of antimicrobial and anticancer agents by providing a greater concentration of metabolites directly to the inside of infected or malignant cells. The greater delivery of drugs within the cells decreases the incidence of drug resistance and thus increases the success of treatment overall. Therefore, it is no surprise that nanoformulations are now becoming essential tools in improving therapeutic efficiency for complex and/or hard-to-treat diseases. (De Jong &Borm, 2020)

Because of how far nanotechnology has come an increased interest will be witnessed in prospective medication based on nanotechnology and nanobiologics. Scientific advancement enables the creation of multifunctional nanoformulations that can deliver medication, image the body, and detect disease simultaneously. This has been greatly improved by using more biocompatible and/or biodegradable materials in order to provide safer products for patients. In addition to these advantages, employing green synthesis for sustainable production of nanoformulations with natural polymers and/or plant-derived substance is becoming extremely popular. Other issues such as regulations, high cost of manufacturing nanoformulations, formulation stability, and conducting long-term safety studies will need to be addressed before nano-therapies can be widely accepted by patients andcommercially successful. In spite of these challenges, nanoformulations will undoubtedly revolutionize the pharmaceutical sciences by enhancing drug efficacy, increasing the precision of therapies and improving patient care. The ability to increase therapeutic levels will assist in creating innovative strategies for treating the diseases of today using modern technologies. (Nikalje, 2021)

Green synthesis is eco-friendly and safe

Greenology has become a sustainable way of producing nanoparticles and pharmaceuticals by utilizing natural biological resources in a safe and environmentally-friendly manner. In contrast to the traditional chemical or physical methods of producing nanoparticles, which utilize toxic chemicals, consume a lot of energy, and produce hazardous waste that can be harmful to human beings and the environment, greenology uses biological materials as reducing and stabilizing agents (reducing and stabilizing agents) when producing nanoparticles. In particular, plants are extremely useful for greenology, since they contain many different types of phytochemicals (such as flavonoids, alkaloids, terpenoids, and phenolic compounds), which help to produce nanoparticles in a natural way. Greenology is therefore an eco-friendly way of producing nanoparticles because it minimizes the use of harmful substances and reduces pollution in the environment. In addition, greenology is a cost-effective, energy-efficient, and scalable process for producing nanoparticles. Because of the benefits of using greenology as a method of producing nanoparticles, more and more researchers are now using it in the fields of nanotechnology, medicine, and pharmaceuticals. The continuing need for sustainable health care and environmental protection has made green synthesis one of the most important areas for scientific research and industrial application. (Iravani, 2017)

The most significant advantage of green synthesis is that it is environmentally sustainable. Conventional ways of synthesizing nanoparticles typically involve using hazardous reducing agents, toxic solvents and subjecting the chemicals to high temperatures, producing assay or waste products that can be harmful to the environment e.g to our soil, air and water, and thereby creating a risk of ecological disaster. Green synthesis reduces the need for harmful chemicals, such as solvents, to make nanoparticles by using naturally occurring plant-based compounds and biological materials instead. Additionally, the green synthesis process generally occurs at lower temperatures and at normal atmospheric pressure (as opposed to the typically high temperatures and low pressures associated with traditional methods), which results in less power/energy consumption and therefore lower operational costs, which are passed onto the consumer of the product. Furthermore, by using plant extracts to act as both reducing agents and stabilizing agents during the synthesis process means that the entire procedure can be accomplished using green synthesis methodology, and it also means that the quantities of chemical waste produced during the entire synthesis will be

minimized. Finally, the renewable nature of biological resources supports the sustainable manufacturing of these products and protects our natural resources. By utilizing green synthesis methods to make nanoparticles, we will also reduce their impact on the environment, which is consistent with the goals of green chemistry and environmentally sustainable industrial development. Thus, green synthesis provides a safer and more responsible alternative to the methods used to produce nanoparticles using conventional methods. (Mittal et al., 2018)

Nanoparticles that are produced through green synthesis, which utilizes plant extracts as opposed to chemicals, tend to be much safer for use in biomedical and pharmaceutical applications. The toxicity levels of nanoparticles produced through biological synthesis will frequently be lower than those from chemical synthesis. Chemical synthesis can leave behind toxic residues on the surface of the nanoparticles. Toxic residues can cause significant harm when they are introduced into the human body. "In contrast, nanoparticles produced using plant extracts will be coated with natural biomolecules, which facilitate the nanoparticles' ability to be implanted into the body, thereby reducing the toxicity associated with implanted medical devices." Because the nanoparticles are coated in natural biomolecules, they may also have improved biocompatibility and reduced toxic reactions compared to chemically synthesized nanoparticles. This makes plants-derived nanoparticles much better candidates for a wide range of medical uses including drug delivery, antimicrobial treatment, wound healing and treatment of cancer. Additionally, because the phytochemicals that are found in many medicinal plants may add to the therapeutic properties of the nanoparticles, the nanoparticles may also have additional antioxidant or antimicrobial activity. Recent reports have shown that green synthesized nanoparticles can exhibit useful biological activity when introduced into living tissue with little or no adverse effects on healthy tissues. As a result, the use of safer green synthesized products in the clinical setting increases their potential for future use in/safely and effectively producing nanomedicines. Overall, green synthesis represents a key aspect of the development of sustainable, patient-oriented, pharmaceutical products. (Ahmed et al., 2019)

Simplicity and cost effectiveness is a major benefit of using green methods for synthesizing nanoparticles. Advanced equipment, expensive chemicals, and complex processes are typical of traditional methods for producing nanoparticles, and create significant costs and limits on commercializing nanotechnology. Traditional methods for producing nanoparticles require advanced equipment, expensive chemicals, and

complex processes, are associated with significant costs, and limit the ability to commercially produce nanoparticles. In comparison, green methods use readily accessible sources for natural material (plant leaves, fruits, seeds, roots, and microbial cultures) as a source of raw materials (biomass) to extract and synthesize nanoparticles. Extraction and synthesis can typically be done quickly (within hours), using mild experimental conditions (ambient temperature and pressure). Green methods are therefore ideally suited for the commercial production of nanoparticles on a large scale in pharmaceutical and industrial markets. The increased use of agricultural waste materials and other residual plant material in green methods will therefore not only reduce the costs of production, but contribute to improved waste management practices. Furthermore, by promoting the use of plant materials for scientific and commercial purposes, green methods support the local and regional rural agricultural economies. The ability of green methods to produce nanoparticles at a lower cost and to have practical applicability are therefore significant factors influencing the growth of the popularity of green methods in nanotechnology research and sustainable manufacturing practices. (Shankar &Rhim, 2020)

Because there is growing awareness of environmental sustainability and a desire for more secure pharmaceutical technologies, the outlook for green synthesis is very optimistic. Researchers are continually engaging in the search for new types of medicinal plants, microbes, or biomolecules to create faster, cheaper, and more efficient nanoparticles with many different functions. Advances being made in biotechnology and nanoscience should enhance the ability to manage, maintain, and reproduce the quality of green-synthesized nanomaterials. While green synthesis has many advantages, there are still issues that need to be explored before harnessing this technology; these include standardizing synthesis protocols, ensuring that the production of these materials is consistent on a large scale, and evaluating their long-term safety. To commercialize green-synthesized nanoparticles safely and effectively in healthcare and industrial markets, there must be adequate regulatory guidance and quality control procedures in place. Nevertheless, green synthesis continues to evolve and is recognized as a novel way of creating new products while protecting our environment, while also improving our lives through advances in science and technology. Green synthesis has several environmentally friendly characteristics, safety, and cost advantages that make it an important part of the future growth of nanotechnology, medicine, and sustainable pharmaceutical industries worldwide. (Roy et al., 2021)

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Herbal nanoparticles are useful in disease treatment

In recent years, there has been increasing interest in the use of herbal nanoparticles in contemporary biomedical science to treat a number of diseases by using medicinal plant-derived bioactive compounds (such as flavonoids, alkaloids, terpenes, etc.). Medicinal plants contain numerous phytochemicals (natural chemicals that are produced by the plants) which are identified as having high therapeutic value; however, many of these compounds have limited solubility, low stability, and low bioavailability limiting their clinical utility. However, nanotechnology can assist with these limitations by converting reconstituted herbal extracts to nanoparticles with enhanced rates of absorption, stability, and targeted delivery. Herbal nanoparticles blend the plant's natural healing properties with advanced drug delivery technologies to optimize the therapeutic effect of the drugs derived from the plants. The nano-sized formability of the nanoparticles allows them to easily penetrate biological barriers and reach the target tissues/cells. Herbal nanoparticles have therefore been extensively studied for their potential use in treating chronic and complex disease processes. Developing a strategy for combining herbal medicine with nanotechnology opens several opportunities in the development of innovative drug development and strategies for managing disease in the 21st century. (Singh et al., 2018)

Herbal nanoparticles represent a major way to deliver an anticancer medication. Curcumin, berberine, and paclitaxel are all plant-based products with proven anticancer activity, but they are not widely used because of their low solubility and rapid metabolism. Formulating these medicines into nanoparticles results in higher bioavailability and uptake into the cell, allowing them to specifically target malignant cells. Herbal nanoparticles have been shown to cause apoptosis, inhibit the growth of tumors, and limit proliferation of malignant cells while minimizing damage to normal tissue. The use of targeted delivery systems increases the amount of drug that accumulates at the tumor site, allowing for treatment with a smaller amount of chemotherapy agent, thus limiting severe side effects, such as nausea, hair loss, and immune suppression. Therefore, herbal nanoparticles represent a safer, more effective method of treating cancer. Numerous preclinical and clinical studies have shown promising results. (Patra et al., 2019)

Infectious diseases caused by viruses, bacteria, and fungi can also be treated with pulse nanoparticles derived from herbal sources through the use of herbal extracts that

contain active compounds. A lot of the plants that have medicinal value are noted for their antimicrobial properties; many of these properties are declines in their stability and ability to enter microorganisms. Through the use of herbal extracts in the formulation of nanoparticles, the activity of these active ingredients will improve, as the surface area has increased and will enable the effective interaction with the microorganism's membrane. This has resulted in more effective disruption of bacterial cell walls and inhibition of bacteria as a result. In addition, there is currently a great deal of ongoing research into the application of herbal nanoparticles for the treatment of antibiotic-resistant infections in patients, which presents a major global health issue. Additionally, research is also being conducted into their use for antiviral treatments of various viral infections, including respiratory diseases caused by emerging viral pathogens. The combined effects of plant substances and nanotechnology on the antimicrobial activity will produce a greater amount of antimicrobial activity and reduce the development of resistance. As a result, herbal nanoparticles can be considered a viable option for the prevention of infectious diseases and for the improvement of health outcomes for the general public. (Ghosh et al., 2020)

Herbal nanoparticles have also been proven to be effective in treating chronic illnesses like diabetes, heart disease, and nervous system diseases in addition to cancer and infectious diseases. Herbal nanoparticles can help to control blood sugar levels by improving the activity of anti-diabetic phytochemicals and improving the body's ability to use insulin to help treat diabetes. They can help to protect the heart by decreasing oxidative stress, inflammation, and cholesterol levels and by developing protective mechanisms to protect heart tissue from damage in heart disease. For neurological disorders like Alzheimer's and Parkinson's, herbal nanoparticles can more easily cross the blood-brain barrier, allowing for the delivery of therapeutic agents to the brain to improve brain function. The enhanced bioavailability and specific delivery of herbal nanoparticles make them very effective at treating chronic illnesses. Additionally, since they come from plants (natural products), they have a lower chance of causing toxicity or side effects compared to synthetic drugs. Pharmaceutical companies are increasingly looking to herbal nanoparticles as a safe and effective way to treat chronic diseases. (Wang et al., 2021)

Through the continued development of nanotechnology, biotechnology, and pharmaceutical sciences, herbal nanoparticles will play a significant role in future treatments for disease. Researchers are working on creating multifunctional

nanoparticles that integrate therapeutic, diagnostic and imaging capabilities. Each of these drugs can provide patients with both immediate and long-term monitoring of the effects of the drugs in their bodies, and can also provide physicians with information necessary to provide targeted treatments. Additionally, researchers are looking into using green synthesis techniques to create environmentally sustainable and biocompatible herbal nanoparticles. Despite the many benefits of herbal nanoparticles, there are obstacles that need to be overcome in order to effectively utilize these therapeutics on a large scale including manufacturing, standardisation, in-depth research necessary for regulatory approvals and long-term safety studies. Before herbal nanoparticles can be used in the clinical setting, there must be significant amounts of clinical trial data to determine the safety and efficacy of these nanoparticles for use in humans; however, with continued research efforts and innovations in technology, there IS great potential for issues to be abated in the very near future. Herbal nanoparticles have the capability to greatly change modern medicine by providing more effective, safer and targeted treatment options for a variety of diseases, ultimately improving patient outcomes and systems of global healthcare. (Zhang et al., 2022)

Conclusion

By merging the fields of pharmacognosy and nanopharmaceutics, there has been a major breakthrough in the evolution of modern-day herbal medicine. Most medicinal plants contain many bioactive and therapeutically relevant compounds however, their clinical efficacy is hindered by a number of factors including low solubility, low bioavailability, instability and lack of targeted delivery. Nanopharmaceutics offer novel solutions to these issues by enhancing the stability, absorption and controlled release of these compounds derived from plants, including a variety of nanocarrier systems e.g. nanoparticles, liposomes, nanoemulsions facilitating site-specific delivery, improved cellular uptake, and reduced systemic toxicity. The combination of these factors will not only improve the efficacy of herbal medicines, but will also greatly reduce side effects, thereby making herbal medicine a more reliable and effective treatment option for use in clinical settings. In addition, through the use of green synthesis techniques, the development of environmentally-friendly and biocompatible nanoformulations has strengthened the safety profile of these nanoformulated herbal medicines. Therefore, the integration of pharmacognosy and nanopharmaceutics creates an outstanding platform to enhance drug delivery systems and has the ability to completely change the way natural product-derived medicine is delivered to patients, as it brings together the

best of traditional medicine with cutting-edge technological advancements and will ultimately result in safer, more effective, and more sustainable healthcare products for patients with a variety of diseases.

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