Targeted Delivery of Natural Products

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Abstract Natural products have been a precious source of innumerable bioactive chemicals due to which many conventional therapies and remedies have been associated with them. Phytochemicals such as alkaloids, flavonoids, glycosides, terpenoids, and many more have contributed significantly to the drug discovery process. Many phytochemical formulations have aided in improving the health status of patients in clinical settings. However, some problems related to the effective delivery of natural constituents to their site of action still exist. These are mainly attributable to the challenging physicochemical and pharmacokinetic characteristics. To address these issues, a lot of research is being conducted that is based upon the interlinking of natural products with nanotechnology. Many studies have shown encouraging outcomes in terms of the targeted delivery of these phytochemicals to their intended sites for the desired therapeutic response using nanocarriers such as metallic nanoparticles, liposomes, and dendrimers, among others. Due to their better tolerability as compared to synthetic chemical entities, natural products particularly the phytochemicals are being explored for achieving delivery through active and passive targeting. This chapter provides an introduction to the formulation barriers of natural products and the recent advances in nanotechnology and formulation science in improving the overall drug targeting to the intended site of action.

Keywords Natural products · Phytochemicals · Targeted delivery · Nanotechnology · Nanoparticles

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1 Introduction

Natural products have been used for centuries by virtue of their vast medicinal uses. The knowledge of traditional medicine has helped the drug developers in devising means for more efficient drug discovery using the phytochemicals. Of all the drugs approved by the United States Food and Drug Administration (FDA) in 2019, around 24% of the drugs were of natural origin (de la Torre and Albericio 2021). Not only plant-based, but animal and microbial origin natural products have also contributed to the development of an effective drug discovery and development process, leading, thereby, to the clinical applications of a series of efficacious molecules. A number of plant-origin drugs have been employed in clinical settings across various medicinal systems. These include Colchicine from *Colchicum autumnale,* Paclitaxel from *Taxus brevifolia,* Hyocyamine from *Hyoscyamus niger,* Morphine from *Papaver somniferum,* and Mitomycin from *Streptomyces caespitosus,* among others (Shah et al. 2020; Shao et al. 2020; Hemati et al. 2021; Bouabdallaoui and Tardif 2022; Sinawe and Casadesus 2022).

Novel, potentially active therapeutic agents are subject to a number of studies to establish their effectiveness in clinical settings. However, their therapeutic delivery remains an uphill task due to the complications in their pharmaceutical presentations including low dissolution profile, stability issues and subsequent problems associated with their pharmacokinetics and bioavailability. Phytochemicals including terpenes, polyphenols, and alkaloids also undergo a higher metabolic processing by the phase II enzymes. This leads to a lesser amount of drug available in systemic circulation, thereby, leading to a decrease in the pharmacological activity of a potential drug candidate (Bose et al. 2020). To cope with these drawbacks, natural product-based nanocarriers since their advent have bridged huge gaps in the targeted drug delivery of these molecules. Based on the principles of targeted drug delivery, these novel mechanisms have been able to target specific receptors, thereby, ruling out the nonselective actions of some natural products such as cytotoxic phytochemicals. This concept is being applied in the lead discovery with natural products of plant origin. Natural product-based nanocarriers have been successfully tested in animal-based models to target the desired sites such as tumors, leading to effective pharmacological profiling of these natural chemical entities. Computational experiments and tools have also confirmed the pharmacological activity of these compounds in silico (Chen et al. 2020). This chapter covers the scope and significance of targeted delivery of natural product-based drugs for maximizing the utility of these bioactive phytochemicals.

2 Natural Products in Medicinal Use

Numerous secondary metabolites with variable chemical structures are produced by a diversity of medicinal plants. These secondary metabolites have played an important part in the discovery and development of drugs. In brief, the plant-based

systems have given rise to a huge number of lead compounds used in both traditional and modern medicine. Cytotoxic agents, including antimicrobials and anticancer agents developed by the study of floral and microbial metabolites as chemotherapeutics, are the chief examples of these molecules. Similarly, a wide variety of compounds have been discovered from sponges, algae and phytoplankton that have supplied a number of leads for drug discovery and development. Discovery of naturally occurring neurotransmitters and active peptides have also proved to be important milestones in therapeutic research.

Ethnopharmacology forms the basis of the medicinal use of plants and other natural sources. Ethnobotany, conversely, is the study of interaction of local plants with the biological aspects of the native people. This term basically deals with the medical applications of an indigenous plant using the inherent knowledge. This helps in imparting the essential parameters that are a prerequisite for the planting of these indigenous botanical sources and their use in day to day life. On the other hand, the broadest definition of ethnopharmacology is "*the interdisciplinary scientific examination of the biologically active compounds that are customarily utilized*" (Leonti 2022). As a result, the ethnopharmacological approach is based upon the merger of pharmacology, chemistry, and botany for attaining therapeutic outcomes in human population. With a very wide scope, field observations, descriptions of the application and biological effects of traditional remedies, botanical identification of plant material, and phytochemical and pharmacological studies form a part of ethnopharmacology. Many researchers have been interested in studying traditional cures and their potential effects for a long time. This has led to significant discoveries that are still playing a vital part in current pharmacotherapy practices (Verma and Singh 2020).

The use of medicinal plants in various ailments has been established. A number of historical accounts have been found in ancient civilizations that provide a record of medicinal use of plants and other natural products for centuries. The rhizomes of *Glycyrrhiza glabra L.*, for instance, are well known for their traditional use as antitussive effects induced by glycyrrhizin, glycyrrhetinic acid, and other phytochemicals. *Papaver somniferum L.* containing alkaloids including morphine, papaverine, and codeine have been used to relieve intense pain as herbal remedy since ancient times. Morphine, a popular and efficacious opioid, was first isolated by Friedrich Serturner in 1803 from poppy plant and continues to be a part of modern analgesic regimens. *Cinchona officinalis L.*, a rich source of quinine, has been a promising medicinal therapy against malaria for centuries (Tisnerat et al. 2021). In Brazilian indigenous medicine, *Achillea millefolium L.* has been used for diuresis in patients with nephropathy and cardiac disease. *Achillea arabica,* a Mediterranean plant, is known to have lipid-lowering activity and has been used in many cardiovascular disorders. *Bidens pilosa L.*, also known as Spanish needles, is a South American herb used as a decoction or tincture, that aids in lowering blood pressure by vasodilation (Michel et al. 2020). *Foeniculum vulgare Mill.*, belonging to *Apiaceae* family, is a traditional herb, the seeds of which are orally ingested to alleviate gastric acidity, constipation and nonproductive coughs. Similarly, *Argemone Mexicana L., Morus albal, Cassia fistula L.,* and *Mentha longifolia L.* are medicinal flora that

exhibit beneficial therapeutic effects in improving the digestion. *Citrullus colocynthis L.,* containing polyphenols and tannins provides relief from urinary problems and jaundice and is used in the form of pharmaceutical powders to treat these ailments. As per the ethnobotanical approach, the plants used for countering bacterial infections for hundreds of years include *Acacia eriloba*, also known as camel thorn, whose infusion helps to treat bacterial pneumonia. The infusions and decoctions of *Abrus precatorius, Artemesia afra, Asparagus africanus*, and *Chrysanthemum segetum L.* provide adequate antitubercular effect and relieve whooping cough (Cock and van Vuuren 2020). *Terminalia glaucescens* extracts have shown activity against various gram-negative bacteria, while ethanolic extracts of *Azadirachta indica* and *Zingiber officinale* show inhibition of growth in *Salmonella typhi* strains (Ugboko et al. 2020). In brief, these and many other medicinal plants form an essential component of the traditional and modern medicine. Figure 1 represents a summary of the diverse traditional medicinal uses of natural products derived from medicinal plants.

Recently, the advent of SARS-CoV-2 lead to dedicated research efforts for the drug discovery and development process using natural compounds. By employing in silico, in vitro, and in vivo approaches, many natural constituents have been investigated that may act as a potential inhibitor of SARS-CoV-2. A few of these components are summarized in Table 1.

In light of these applications, it can be established that the natural products encompass a vast family of varied chemical substances that may be produced by any organism or may originate from a mineral source. They possess a wide range of

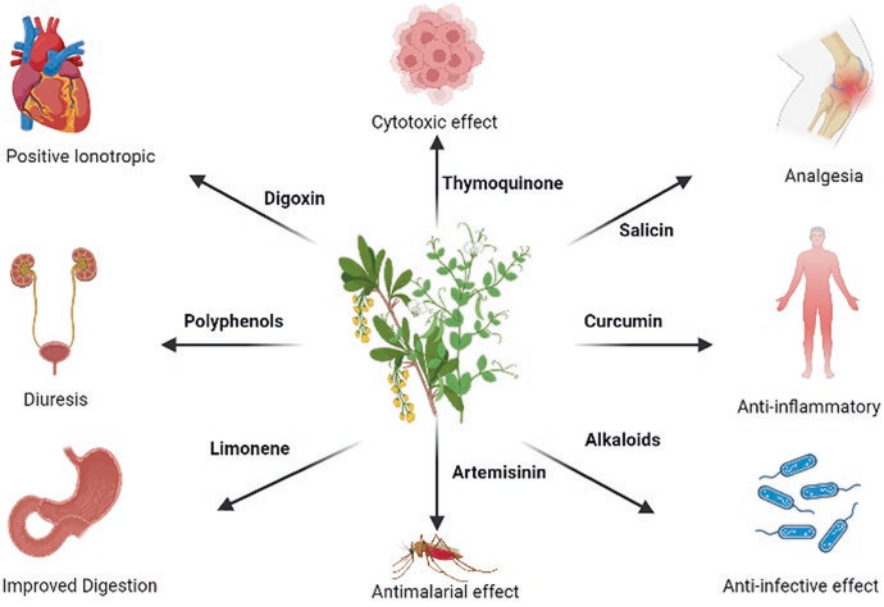

Fig. 1 Medicinal uses of the plant-based natural products and constituents

Table 1 Natural lead compounds having potential activity against SARS-CoV-2

Natural compound	Chemical class	Botanical source	References
Amentoflavone	Flavonoid	*Torreya nucifera*	Orhan and Senol Deniz (2020)
Chrysin	Flavonoid	*Oroxylum indicum*	Shah et al. (2021)
Quercetin	Flavonoid	*Lactuca sativa L.*	Gasmi et al. (2022)
Quercetin-3-O-rutinoside	Glycoside	*Dysphania ambrosioides*	da Silva et al. (2020)
Lycorine	Alkaloid	*Lycoris radiata*	Jin et al. (2021)
Baicalin	Flavonoid	*Scutellaria baicalensis*	Wu et al. (2020)
Berberine	Alkaloids	*Coptis chinensis*	Wink (2020)
3,7-di-O-methyl-kaempferol	Flavanoid	*Siparuna cristata*	Leal et al. (2021)
Lactucin	Sesquiterpene	*Cichorium intybus L.*	Ávila-Gálvez et al. (2022)
Hispidulin	Monomethoxyflavone	*Artemisia sublessingiana*	Jalmakhanbetova et al. (2021)

biological activities and unique pharmacological effects. Natural products have historically been important in the drug discovery process. This importance is further established owing to their use in traditional remedies. Natural products have been used for centuries as common remedies, and in recent years, the scientific community has turned its attention to them as a result of mounting data linking them to health advantages and the prevention of numerous diseases. Recently, their significance has again started to increase as masses are turning toward naturopathy apparently considering the ill-effects of the synthetic chemicals. The major challenge, however, associated with discovery of bioactive compounds is to establish a drug delivery methodology that ensures that adequate amount of the therapeutic agent reaches the site of action. The formulation development of phytochemicals is a laborious process and incorporates a series of steps. Following, the early screening of the crude extract and extraction of specific metabolites, the identification process of natural product is started. This involves the structure elucidation processes including Mass Spectrometry and Nuclear Magnetic Resonance among others. Thereafter, in vitro and in vivo screening of the biological activities of the isolated compound is initiated. Preclinical studies based upon animal models to unveil the early information regarding the pharmacokinetics and pharmacodynamics of the active molecule are carried out. Once validated, formulation engineers develop a diverse series of formulations that can potentially be employed for human testing. During these preclinical trials, not only is the natural compound tested for its effectiveness but the best formulation options available are also selected. Marketing of the drug after approval and subsequent post marketing surveillance is then carried out as the last, yet continuous, step of the process (Mushtaq et al. 2018).

Conventionally, the crude drug from natural sources is subjected to extraction processes using various solvents based upon the physicochemical properties of the

constituents. These mixtures are then processed for fractionation and final formulation. These can be in the form of tinctures, i.e., the extracts of series of diverse compounds based upon their miscibility in water and alcohol like tinctures of *Cannabis sativa*. Similarly, decoctions which are extracts prepared by heating a medicinal crude drug in water for a given time interval to extract out its principal chemical substances like the decoction of *Panax ginseng* and *Glycyrrhiza uralensis*. Pastes, a semisolid formulation of natural products containing about half of solid powdered content of the crude drug levigated in a fatty base are also very common. Herbal teas comprising of infusions of comminuted herbs such as *Camellia sinensis* have been used for symptomatic relief for centuries. Similarly, liniments which are the preparations rubbed on skin for provision of warmth and pain alleviation, for instance of *Capsicum annuum*, are often employed for pharmacological benefits (Pengelly 2020).

3 Contemporary Approaches to Formulation Development of Natural Products

Natural products are accepted as one of the most significant components of both the traditional and modern medicine owing to their benefits and diverse biological activities. However, developing them into clinical candidates has been hampered by a number of problems including pharmaceutical issues like poor solubility, limited permeability, and poor chemical stability. These formulation problems may affect the bioavailability of these compounds and may lead to their therapeutic failure. Stability of a potential drug molecule in the systemic circulation also restricts its efficacy and leads to early degradation of molecule before reaching the target site. In order to get over these obstacles, novel drug delivery systems can be developed to enhance the stability, dissolution, therapeutic efficacy and selectivity of a given natural drug candidate (Almeida et al. 2022; Rego et al. 2022).

The advent of nanotechnology has provided various targeted drug delivery options including metallic nanoparticles, liposomes, micelles, nanotubes, dendrimers and quantum dots among others. These systems have largely improved the pharmacological properties of these natural products. These systems targeted toward a specific receptor site to improve the pharmacological aspects of natural product formulations have been widely accepted both in basic and clinical applications. Of these, passive drug targeting of phytochemicals to the tumor microenvironment (TM) follows the application of nanotechnology in formulation development. It is well known that following an intravenous administration, the enhanced permeability retention (EPR) effect causes macromolecules to reach and accumulate in the solid tumors more than they do in the healthy tissues. This EPR effect has gained popularity over the past years as it has been used to enhance the delivery of medicines by nanoparticles for solid tumor diagnosis and treatment using the concept of passive drug targeting. Due to an imbalance of growth factors and mediators, the

vasculature contains endothelial gaps and becomes quite leaky. These leaky vessels could be used for passively targeting the solid tumor as nanoparticles can reach there and a better retention can be expected due to impaired drainage of lymphatics at tumor sites. Passive targeting involves spontaneous entry or diffusion of drug-loaded nanocarriers into the tumor microenvironment. In comparison, as represented in Fig. 2, the active targeting involves the formulation of nanocarriers decorated with a specific surface ligand that helps reaching the binding site, tumor site or site of injury more readily due to a its higher affinity for it, thereby, producing a targeted extravasation of the drug-loaded nanocarrier at the particular site. A number of tissue injuries have been reported to be relieved after coupling of nanomedicine and EPR effect (Narum et al. 2020).

The widely accepted novel drug delivery systems, employing active or passive targeting approach, that have gained a widespread popularity are nanoparticles. Their size ranges from 1 to 100 nm approximately and may exploit the EPR effect for targeted natural product delivery. The use of nanoparticles in target-specific therapeutic activity may prove promising due to better physical and chemical characteristics. Green synthesis or biogenic synthesis is a method that utilizes the concept of using extracts or chemicals derived from natural sources to produce nanoparticles for the purpose of stabilization via either a bottom-up approach, i.e.,

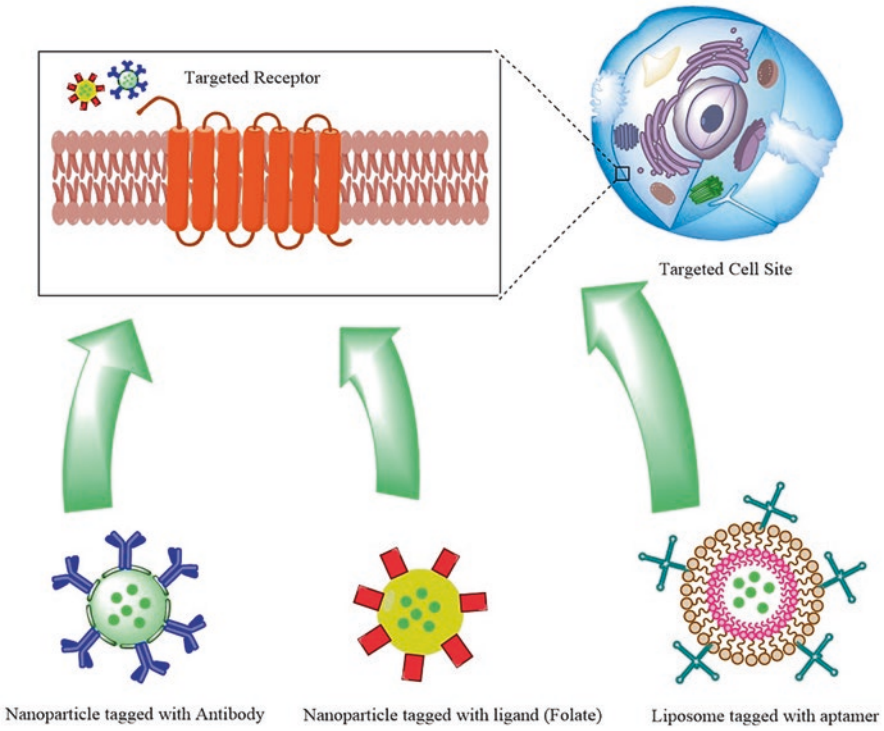

Fig. 2 Active targeting of nanocarriers toward the desired receptor

assembling small atoms or molecules into larger entities or a top-down approach by splitting a larger sized particle into tiny particles. The plant extract containing the phytochemicals, for instance polyphenols, terpenoids or other chemicals, is added in the solution containing metal ions which we want to use for the synthesis of nanoparticles. Several metallic nanoparticles (MNP) could be synthesized through green synthesis including silver, zinc oxide, gold, palladium, platinum and copper nanoparticles (Jadoun et al. 2021). Plant sources reported to contribute effectively in green synthesis of MNPs include, but are not limited to, *Moringa oleifera Lam.* (leaves), *Acorus calamus L.* (rhizome), *Aerva lanata (L.)* Juss. (whole plant), *Allium sativum L., Curcuma longa L.* (powder), *Artemisia haussknechtii Boiss.* (leaf), and *Mirabilis jalapa L.* (leaf) (Maghimaa and Alharbi 2020; Alavi and Karimi 2020; Puthur et al. 2020; Palithya et al. 2021; Paiva-Santos et al. 2021).

Silver (Ag) nanoparticles have been reported to possess efficient cytotoxic activity against cancer cells. Due to the nanosize range, they passively target tumor sites and have been reported to be effective on a number of cell lines including human lung epithelial A549 cells, MCF-7 human cell line, HepG2 cell line, and HCT116 cell line (Sankar et al. 2013; Abootalebi et al. 2021; Raj et al. 2020; Deepika et al. 2020). Their anticancer effect has been related to genotoxicity, cell cycle arrest, and anti-angiogenic properties of Ag nanoparticles. It was also revealed that Ag nanoparticles are involved in the generation of free radical species leading to disruption of mitochondrial processes and, ultimately, cell death (Ratan et al. 2020; Lima et al. 2022).

Recent studies have established the role of Gold (Au) nanoparticles in anticancer therapy. They have been proven to be safe carriers for passive as well as active targeting of natural products toward the binding sites. They have negligible toxicity, high biocompatibility and demonstrate rich surface reduction by phytochemicals. The effect of Hesperidin conjugated Au nanoparticles were studied in human triple-negative breast cancer cell line MDA-MB-231, which emphasized the antitumor potential of these nanoparticles along with their role in activation of macrophages in eradicating tumor cells effectively rendering them as a novel option in anticancer therapy (Sulaiman et al. 2020). Another study unveiled that quercetin-conjugated Au nanoparticles were very functional in case of inducing apoptosis in hormone-dependent MCF-7 cell lines. Furthermore, the epidermal growth factor receptor signaling pathways involved in unregulated cell proliferation were also inhibited (Khan et al. 2021).

Apart from the MNPs, liposomal form of phytochemicals like curcumin has proven to have a significant cytotoxic activity against cancers. Curcumin-loaded liposomes and nanoparticles have been reported to arrest the uncontrolled cell division in prostate cancer cell lines and cervical cancer cell lines respectively (Kashyap et al. 2021). D Kong et al. reported that Resveratrol plus epirubicin-loaded liposomes modified with wheat germ agglutinin (WGA) demonstrated a promising cytotoxic effect, as compared to only epirubicin-loaded liposomes, in the C6 glioma cells cytotoxicity assay after about 48-hour incubation period. The Resveratrol plus Epirubicin liposomal formulation was also targeted in vitro for avascular C6 glioma

spheroids. A notable effect was produced as not only the volume of tumor spheroids was reduced, but most of tumor cells also underwent lysis (Kong et al. 2022).

Antibody–drug conjugates have also been effectively applied for the active drug targeting of cancer cells. This idea is widely adopted for natural products as well. Eribulin, a derivative of Halichondrin B, is a natural constituent obtained from *Halichondria okadai,* a marine sponge. Halichondrin B has been found to be effective against various solid tumors and has been used for the formulation of an antibody–drug conjugate. The formulation is currently under investigation in phase II clinical trials to establish its efficacy (Newman 2021). Similarly, studies are underway to study the active targeting of natural chemical constituents using hyaluronic acid labeled nanocarriers. Hyaluronic acid has affinity for CD-44, a protein overexpressed in many cancers. Hence, CD-44 receptor is a target through which the natural compounds can be specifically delivered in the cancer cells. A recent study exhibited that the hyaluronic acid decorated thymoquinone nanoparticles showed a marked cell death in triple negative breast cancer cell lines MDA-MB-468 and MDA-MB-231. This activity was also confirmed in in vivo study in mice model which recorded a decrease in tumor mass after inoculation of these nanoparticles (Bhattacharya et al. 2020). Figure 3 provides an insight into the process of active and passive targeting of cancer cells. Similarly, another study stated that the hyaluronic acid conjugated nanoparticles with curcumin, actively target the cancer cells. These nanoparticles did not only provide controlled drug release but the cell growth was also inhibited effectively in the human cancer cell lines, i.e., A549, PANC-1, HCT116, and Caco-2 cell lines (Malaikolundhan et al. 2020; Thummarati et al. 2021).

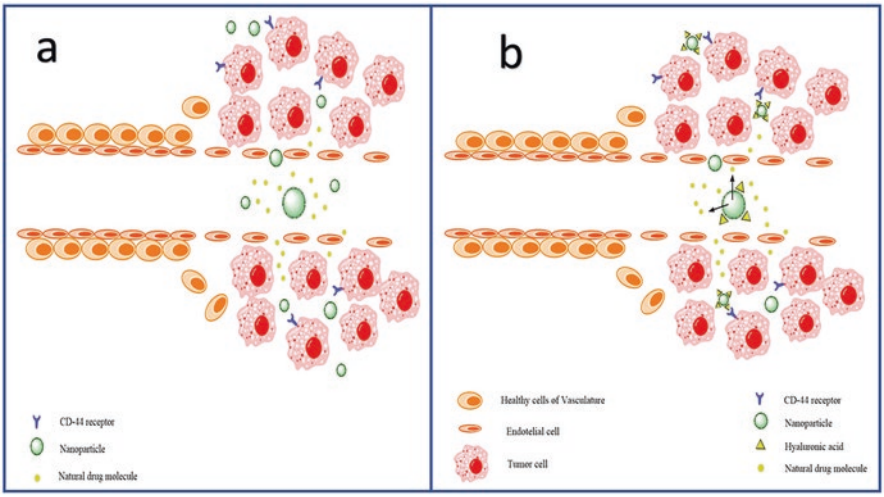

Fig. 3 (**a**) Passive targeting of nanoparticles with natural constituents toward tumor cells exploiting the EPR effect (**b**). Actively targeted natural drug-loaded nanoparticles labeled with a ligand (Hyaluronic acid) reaching the targeted receptor site of tumor cells, CD 44 receptor

For the pharmacotherapy of Alzheimer's disease (AD), dedicated research studies are underway to identify the phytochemicals that can specifically target the mechanisms involved in the disease progression. The major challenge lies in the delivery of the natural products to the target site by crossing the Blood Brain Barrier (BBB). Hence, nanodrug delivery systems have been employed in order to cope with such issues. Exosome-like liposomes (<200 nm size), for instance, have been loaded with curcumin from *Curcuma longa* and tested for their neuroprotective activity in the human neuroblastoma cell lines SH-SY5Y. They halted the oxidative stress, hence exhibiting their antioxidant and anti-inflammatory activities. This has been confirmed in vivo studies using zebrafish embryo model (Fernandes et al. 2021). Similarly, a glycoside, Luteolin-loaded chitosan nanoparticles have been studied for the protective effects in AD. In vivo studies in mice model exhibited the improvement in space-related memory by providing an improved antioxidant effect along with reduction in neuroinflammation by retarding neurofibrillary tangle formation at molecular level (Abbas et al. 2022). In another study, female Swiss mice were injected with amyloid peptide to induce Alzheimer's disease. Lipid-core nanocapsules loaded with Chrysin, obtained from *Passiflora caerulea,* were prepared and the mice were administered with the formulation. The findings exhibited that the neuroinflammation was reduced up to a significant extent. The brain-derived neurotrophic factor (BDNF) level was upheld along with reduced oxidative damage in prefrontal cortex of the brains of mice (Giacomeli et al. 2020). In addition to AD, targeted drug delivery of phytochemicals has also been studied in other neurodegenerative conditions. The extract of plant *Aphanamixis polystachya*, loaded in liposomal formulation has been tested for its anti-Parkinson's activity in mouse model. The principal constituents, including 2-Pentanone, 5-hydroxypipecolic acid, and beta-elemene in liposomal carrier, successfully provided targeted drug delivery and provided pronounced neuroprotective and anti-inflammatory effects. The positive changes in the behavior of mice along with betterment of their locomotion were also observed (Shariare et al. 2020).

The targeted delivery of phytoconstituents also attenuates bacterial infections to a significant level. Recently, the zinc nanoparticles synthesized using the leaf extract of *Aloe socotrina* proved to possess effective antibacterial potential against *Pseudomonas aeruginosa* and *Proteus vulgaris* at concentrations of 50 μg/mL and 75 μg/mL. Bactericidal effect was also observed for *Klebsiella pneumonia* and *Escherichia coli* at higher concentrations. These nanoparticles are described to disrupt the bacterial cell membranes and subsequent killing of bacteria (Fahimmunisha et al. 2020). Similarly, palladium nanoparticles synthesized by using *Rosmarinus officinalis* extract have shown significant antibacterial and antifungal activity both in vitro and in vivo (Rabiee et al. 2020). While considering the clinical and regulatory processes, the natural product-based nanoformulations aimed at targeted drug delivery of these actives have acquired the attention in the global market. They are being employed in routine clinical use at a number of settings internationally. Table 2 summarizes a few marketed brands based upon natural product nanoformulations.

Table 2 Marketed nanoformulations for the targeted drug delivery of phytochemicals

Marketed product name	Natural product formulation	Manufacturer	Actions	References
Abraxane®	Nanosuspension of human serum albumin protein loaded with paclitaxel	American BioScience (USA)	Treats breast cancer after failure of prior chemotherapies	Yuan et al. (2020)
PICN®	Paclitaxel injection mixture for nanodispersion	Sun pharma advanced research co., ltd. (Mumbai, India)	Attenuation of breast cancer	Ma et al. (2021)
Bepanthol ultra facial protect Cream®	Lecithin, ceramides, niacin, Dexpantenol, glycine, glycerine, etc. dispersed in nanoemulsion	Bayer HealthCare (Spain)	Moisturizes the skin, prevents aging of skin	Cardoza et al. (2022)
Nouriva repair moisturizing Cream®	White petrolatum, zinc oxide, lanolin, liquid paraffin, glycerin, lecithin, glycolic acid, allantoin, etc. loaded nanoparticles	Ferndale laboratories, Inc. (United States)	Provides moisturizing effect to the skin	Kaushik and Kumar (2020)
Marquibo®	Vincristine Sulfate loaded liposomes	Talon Therapeutics Inc. (United States)	Attenuates Hodgkin and non-Hodgkin lymphoma	Shahin et al. (n.d.)
Identik masque floral repair®	Seed extract of *Punica granatum* and hydrolyzed yeast	Identik (France)	Provides repair to the hair	Kaul et al. (2018)

4 Opportunities and Challenges in Targeted Delivery of Natural Products

On the landscape of natural drug development, the accumulation of natural products and nanotechnology has made a significant breakthrough over the past decades. This paradigm shift has provided more effective drug delivery at the intended site of action with less hazardous effects, thereby, resulting in the development of efficient therapeutic options especially in neoplastic diseases for specifically targeting the tumor cells. However, there is still a long way to go before it is adequately streamlined for acceptance at both preclinical and clinical phases.

A number of factors determine the in vivo behavior and efficacy of the nanocarriers encapsulating a natural constituent desired for targeting. The physicochemical characteristics of the carrier as well as the charge induced on the its surface, the specific polymer or metallic group used in formulation, and any particular functional group decorated on the surface of the carrier may affect its stability within the bloodstream. One of the major problems is that the circulation half-life of the nanocarrier may not be too sound to reach the desired target due to their rapid clearance

by the reticuloendothelial system. This may lead to early exit of the nanocarriers from the bloodstream of the patient and, hence, failure of the drug delivery system. Efforts are currently underway to optimize the circulation half-life of the nanocarriers for productively reaching the target. A number of techniques including stealthing of nanocarriers by polyethylene glycol (PEG) or related chemicals and nanosizing further to refine the pharmacokinetics are currently being tested clinically (Yadav and Dewangan 2020). In addition, these drug delivery systems intended for active targeting of the cells may contain peptides or proteins that might make them mimic a biological entity. They can, hence, be considered as antigens or immunogens by the immune system, thereafter initiating a hypersensitivity response or related toxicities (Kashyap et al. 2021; Muzammil et al. 2023).

Translation of safety and effectiveness observed during preclinical studies into clinical applications remains one of the most daunting tasks for the drug developers. Many compounds and drug delivery systems may prove to be efficient in reducing the overall disease presentations in preclinical studies; however, when employed to clinical conditions, these pharmacological systems do not show any significant potential. While studying the EPR effect in cancer models, for instance, there may exist a significant difference in EPR effect in human subjects with cancer and in vivo models. Another hurdle is the interindividual genetic and clinical differences, that may also hinder the selective targeting of the nanocarrier loaded with natural compounds. Every tumors environment differs, and hence, the pharmacological properties of various nanocarriers may also vary. Moreover, many studies have revealed that the nanocarriers may require a synchronization of their physicochemical features as per the type of individual or patient in order to ensure maximum bioavailability. Developing natural product-based personalized nanomedicines, hence, needs to be exploited for attaining effective clinical outcomes (Narum et al. 2020).

5 Conclusion and Future Perspectives

The association of natural products and nanomedicine has imparted very promising outcomes in the field of contemporary pharmacotherapy research. Many problems such as the toxicities of synthetic chemical entities and their processing schemes have been overcome by employing phytochemicals having adequate pharmacological activities against various diseased conditions. The recently developed systems have proved to be effective in a number of in vivo studies and ongoing clinical trials and have exhibited targeted delivery of the natural constituent to the desired receptor sites without any notable nonselectivity and toxicity. However, scalability, safety, effectiveness, and cost management still remain major challenges before these natural products can be translated for targeted delivery in clinical conditions. Moreover, more focused research in the field of nanotechnology in tailoring the nanocarriers as per the individual factors may be done for developing improved natural product formulations based on the idea of precision medicine. A large number of natural

products can be made to target specific cell and tissue types by the concerted efforts of pharmacognosists, pharmacologists, and formulation developers by the employment of advanced technologies.

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