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Review Article

Nanomedicine Based on Natural Products: Improving Clinical Application Potential

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Natural products have antitumor, anti-inflammatory, antioxidant, and other pharmacological activities and are an important source of drugs for prevention and treatment of various diseases. However, the inherent defects of natural products in physiological media such as poor solubility and stability and short biological half-life limit their clinical application. In recent years, more and more attention has been paid to the science of drug delivery by nanoscale materials. A large number of in vitro and in vivo studies have further confirmed the efficacy and safety of nanomedicine based on natural products in preclinical models of various diseases. In this review, we summarized the achievements of nanomaterials in improving the efficacy of natural products, introduced the research progress in several key fields of natural product-based nanomedicine in medical application, and discussed the challenges and prospects of clinical transformation of nanomedicine.

1. Introduction

In discovering lead compounds to treat various human diseases, natural products from plants, animals, and microorganisms provide rich sources for novel compound identification [1]. It is generally believed that compared with synthetic compounds, the structure of natural products is diverse [2]. In addition, most natural products show strong biological activity, optimal adsorption, good distribution, adequate metabolism, and elimination characteristics, which are more similar to drugs compared with synthetic compounds [3]. For multifactorial and complex diseases, different natural products activate a variety of signal transduction pathways to treat diseases by regulating multiple targets, which has more therapeutic potential than drugs aimed at a single site [4]. Therefore, natural products not only contain excellent precursor structure but also provide direct treatment. At present, there are 2 million species of plants, animals, microorganisms, and fungi, of which 95% have not been evaluated for biological activities [5]. Due to the high costs and development associated with synthetic compounds and a wide range of natural products, additional valuable and bioactive natural products need to be uncovered. Thus, natural products are worthy of attention since they exhibit great potential for the discovery, development, and application of drugs.

Although the pharmacological activity and therapeutic potential of natural products for human diseases are recognized, the application and development of natural products are limited by their susceptibility to physiological media and low bioavailability. The emergence of nanotechnology provides an effective strategy for efficient delivery of natural products to adapt to valuable clinical applications by improving bioavailability, targeting, and controlled release [6](Figure 1).

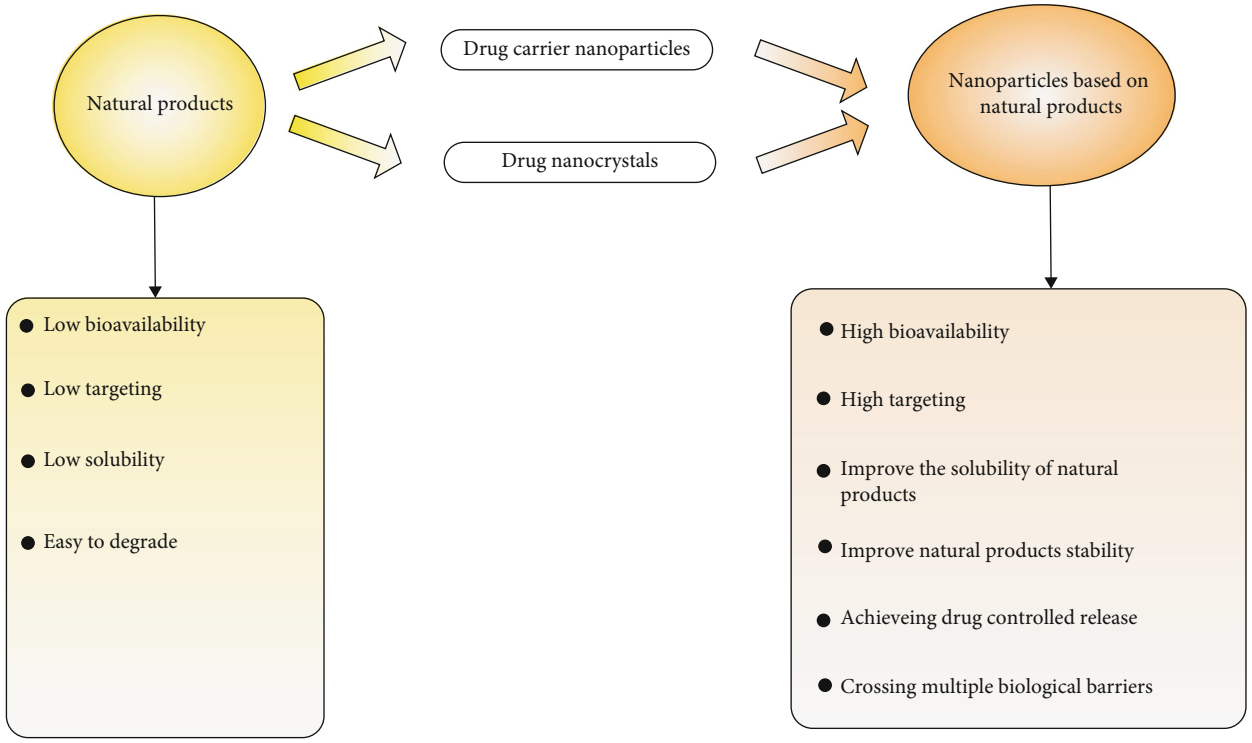

Figure 1: Inherent defects of natural products and advantages of natural product nanoparticles.

2. Historical Review of Drugs Derived from Natural Products

Plant-derived natural products have played a leading role in drug development since plants are easy to obtain. Early humans recognized the therapeutic role of plants when trying to treat diseases. These plants have proven to have medicinal value in practice, as they are present in a number of recorded documents [7–9]. So far, about 60% of the pharmaceutical preparations in the market are derived from botanical natural products and about 80% of the world's population depends on traditional botanical drugs [10]. "Hot" drugs attracting international attention include the anticancer drug paclitaxel and its derivatives, the antimalarial drug artemisinin, and the cardio-cerebrovascular drug ginkgolide.

As a substance inhibiting the proliferation of microbial competitors and other pathogenic microbes in the environment, antibiotics are widely used to fight infectious diseases [11]. Natural products from microbes play an important role in the discovery and development of antibiotics. Most antibiotics with therapeutic activity are natural products derived from microbes [12]. Since the British bacteriologist Alexander Fleming discovered penicillin, the world's first antibiotic, in 1928, it has ushered in a golden age of natural products derived from microorganisms to treat human diseases. Of course, microbial products are not limited to antibiotics, as a single microbe can produce up to 50 secondary metabolites that can be used to develop antiviral drugs, anticancer agents, and immunosuppressants [13].

It is known that the ocean covers more than 70% of the earth's surface, representing 90% of the biosphere volume. Due to the limitations in science, technology, and human cognition, drug discoveries based on natural products mainly depended on terrestrial organisms. Therefore, natural products derived from marine organisms are a neglected treasure [14, 15]. In the late 1980s, improved science, technology, and modern bioengineering, individuals began to pay more attention to marine organisms [16]. The marine environment is quite different from the terrestrial environment, since these organisms face high pressure, high salt concentrations, low temperatures, and low oxygen levels. During the course of long-term evolution, marine organisms formed different metabolic modes and adaptation mechanisms from terrestrial organisms. Some secondary metabolites with novel structures and significant pharmacological and toxicological effects were produced. Presently, many breakthrough achievements have been made in the development of marine drugs. Scientists have isolated a series of new compounds with antibacterial, antiviral, anti-inflammatory, antitumor, and other biological activities from marine organisms such as algae, sponges, starfish, and echinoderms [17–20]. The chemical structure novelty and pharmacological activity of marine bioactive natural products are unmatched by terrestrial organisms, and it has become one of the main directions in the development of new drugs [21].

3. Nanostrategy of Drugs from Natural Products

Nanometer-sized particles exhibit unique properties and functions. Clinical experience shows that the application of nanoparticles increases the accumulation of active ingredients in lesion sites, weakens the systemic toxicity of drugs, promotes the solubility of insoluble drugs, improves the

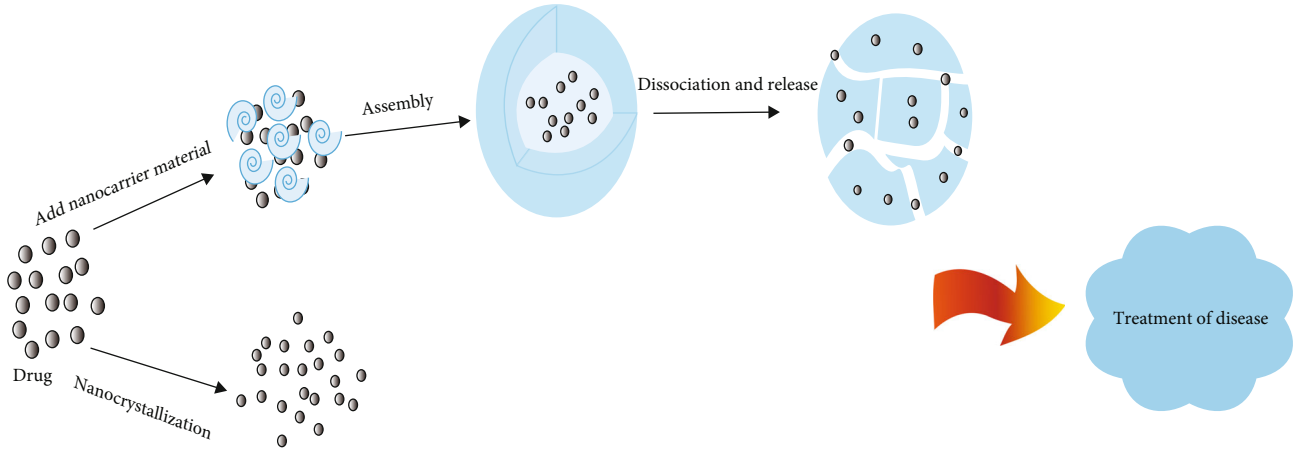

Figure 2: Nanomedicine therapy strategies based on natural products.

stability of drugs *in vivo*, and reduces drug resistance [22]. The size of nanodrugs is usually less than 1000 nm. One technique includes drug loading by nanoparticles, which physically wraps pharmacologically active compounds inside or chemically attaches them to the surface. Types of nanocarriers mainly include lipid nanoparticles, nanoemulsions, polymer nanoparticles, inorganic nanoparticles, and biological nanoparticles [23]. The second type includes pure nanomaterials, which directly use nanoparticles as diagnostic and therapeutic agents; this can be used not only as a carrier but also as a therapeutic drug (Figure 2). Traditional drug treatment lacks effectiveness and site specificity and is inefficient in controlling disease progression and frequent drug administration, resulting in additional adverse effects. Therefore, the research and development of nanodrugs are particularly important.

Many isolated natural products show strong pharmacological activities including antitumor, anti-inflammatory, antioxidant, and other beneficial effects as proven *in vitro* [24–26]. However, most natural products show limitations such as low hydrophilicity, instability, quick metabolism, low bioavailability, or poor permeability. As a consequence, the *in vivo* effects of these drugs are not ideal and require repeated dose administration beyond the safe range, which is unfavorable in the cases of long-term treatment for chronic diseases [4]. Nanotechnology represents a new method to overcome these challenges. The development and application of nanotechnology have greatly promoted the therapeutic efficacy, safety, and patient compliance for drugs derived from natural products. Without a doubt, the combination of natural products and nanotechnology will have great advantages in health care in the future. At present, cancer, diabetes, neurodegenerative diseases, cardiovascular diseases, and other diseases pose serious challenges to global health. This article reviews the application of nanodrugs derived from natural products and their use to treat human diseases.

4. Application of Nanodrugs Derived from Natural Products

4.1. Application of Nanodrugs Derived from Natural Products Used to Treat Cancer. The incidence and mortality rates for cancer are increasing yearly worldwide. According to the International Agency for Research on Cancer, about 18 million new cancer cases and 9.6 million cancer-related deaths were reported worldwide in 2018. It is expected that the number of new cancer cases and related deaths will increase to 20.3 million and 13.2 million, respectively, by 2030 [27, 28]. Therefore, cancer is expected to become a major threat to human health in countries around the world and is a block on the road to long life expectancy [28].

Even though cancer has been effectively treated using surgery, radiotherapy, and chemotherapy, the systemic side effects caused by chemical drugs cannot be ignored. Obvious side effects include hair loss, vomiting, hypertension, heart disease, and arterial thromboembolism [29]. The advantage of natural products lies in their multitarget and multimechanism antitumor effects, which can modulate the cancer microenvironment and diverse cell signal cascades. Some natural products have the ability to can induce apoptosis and autophagy in tumor cells such as quercetin, silymarin, taurine, melatonin, and astaxanthin. Others, such as curcumin, lycopene, piperine, epigallocatechin-3-gallate, and vitamin D, treat cancer by regulating embryonic developmental pathways (Notch pathway, Wnt pathway, and Hedgehog pathway) [30]. At present, a variety of *in vitro* and *in vivo* experiments show that compared with other synthetic chemotherapy drugs, natural products have comparable anticancer efficiency and lower side effects [31, 32].

Even more surprising, natural products can reverse or bypass drug resistance in tumor cells by regulating drug-resistant proteins and targeting nonapoptotic cell death [33]. In addition, the size and surface modifications of nanoparticles also play an important role in tumor therapy. On one hand, due to the existence of enhanced permeability and retention effects (EPR), nanoscale drugs tend to gather in tumor tissues. On the other hand, the surface functionalization of nanoparticles can target specific cancer cells and improve the localization and efficacy of drugs [34](Figure 3).

For example, camptothecin (CPT) is a cytotoxic quinoline alkaloid isolated from bark and branches of Camptotheca acuminata grown in China. Its anticancer activity was approved by the U.S. Food and Drug Administration

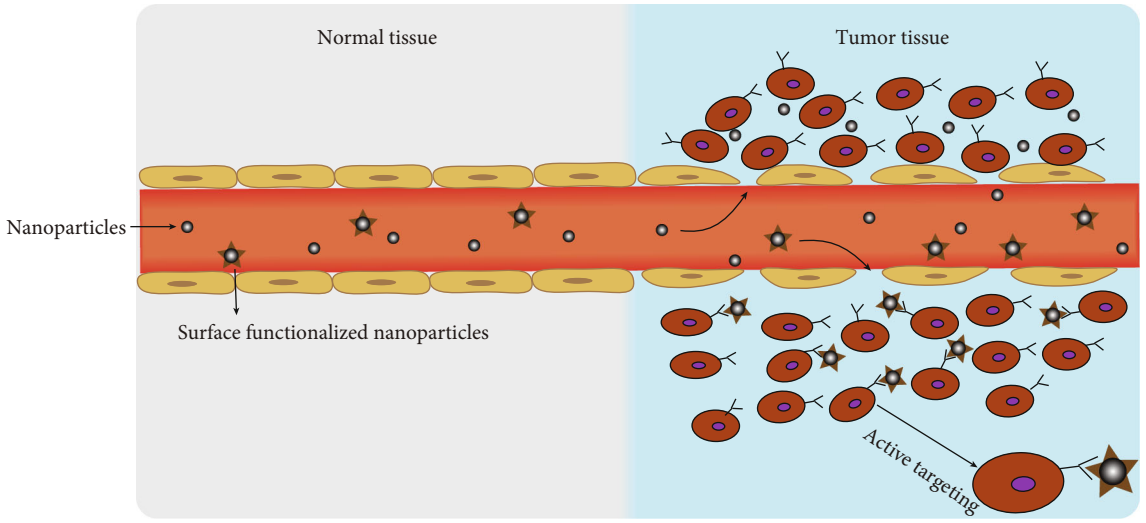

Figure 3: EPR effect of nanoparticles in tumor tissues and targeting of surface functionalized nanoparticles.

(FDA) and is widely used for the treatment of a variety of tumors [35].

Research on the anticancer mechanisms of CPT has promoted the emergence of a large number of CPT derivatives and analogues, including irinotecan, topotecan, and 10-hydroxycamptothecin [36]. Even though this has greatly improved the inherent defects of maternal drugs with good antitumor activity, there are still many problems in their clinical application, such as systemic toxicity and low tolerance. In order to overcome these problems, scientists try to combine nanotechnology with traditional medicine to improve therapeutic effects. In designing camptothecin-based nanodrugs, most are based on nanocarrier-assisted drug delivery, carrier-free nanodrugs, and prodrugs coupled with nanodrug delivery. Among these, the typical nanopharmaceutical is CRLX101, which is a type of CPT nanoparticle based on cyclodextrin. Gaur et al. [37] reported the therapeutic effects of CRLX101 in phase 1/2a clinical trials on patient samples with advanced solid malignancies. Results showed that CRLX101 significantly inhibited tumor cell proliferation and angiogenesis, but also decreased the expression of topoisomerase-1, Ki-67, CaIX, CD31, and VEGF. Compared with CPT and its derivatives, CRLX101 showed better tolerance, safety, efficacy, and pharmacokinetic characteristics [38]. To understand the nanosizing of anticancer drugs, Zhao et al. [39] combined the two different anticancer drugs 10-hydroxycamptothecin (HCPT) and doxorubicin (DOX) into a single drug delivery system through a self-assembly method to understand the combination therapy of carrier-free pure nanodrugs. The preparation of this dual-drug nanoparticle is not only simple and convenient but also the water solubility of the HCPT is increased 50 times after self-assembly, and the intracellular DOX retention is increased 2 times, showing higher chemosensitivity and inhibition of drug-resistant cancer cells. In addition, conventional wisdom emphasizes that cells are not able to fully uptake fibrillar structures. Both *in vitro* and *in vivo* studies have proven that nanofibers formed by coupling the anticancer drug CPT with polypeptides can effectively inhibit the growth of tumor cells by overexpressing integrin. This new prodrug delivery system provides a novel research direction for tumor-targeting drug delivery [40].

Berberine (BBR) shows antiacute myeloid leukemia activity *in vitro*. To improve the solubility of BBR, researchers designed a self-nanoemulsifying system containing BBR (BBR SNE). This system helps enhance penetration and prevents outflow of BBR, which significantly improves relative oral bioavailability of BBR and greatly improves the efficacy against acute myeloid leukemia. The particle size of this system is approximately 23.50 ± 1.67 nm [41].

Phycocyanin (C-PC) is a water-soluble phycobiliprotein that can be used as food. It is believed that phycocyanin prevents the development of cancer through multiple mechanisms and has potential as an antitumor drug with high efficiency and low toxicity [42]. However, poor stability limits the development and application of the molecule. Yang et al. [43] constructed PH-sensitive carboxymethyl chitosan-CD59-specific ligand peptide nanoparticles to deliver C-PC, which can effectively target HeLa cells and slow-release drugs for anticancer effects.

4.2. Application of Nanodrugs Derived from Natural Products Used to Treat Diabetes Mellitus. Diabetes is a chronic metabolic disease caused by defective insulin secretion or impaired biological effects. Long-term high blood glucose levels may damage macrovessels and microvessels and endanger the heart, brain, kidney, eyes, and feet, leading to other diseases such as cardiovascular diseases, chronic kidney disease, retinopathy, and lower limb necrosis [44]. Diabetes cannot be cured and long-term use of synthetic antidiabetic drugs increases the risk of adverse reactions. In addition, the increased prevalence of diabetes and the threat of related complications prompt the discovery of new safe drugs. A study found that some natural products show great potential in treating diabetes and its complications, and the application of nanotechnology enhances the benefits of natural products in the treatment of disease. The nanocarrier

protects loaded natural hypoglycemic agents from rapid clearance *in vivo*, thus, optimizing the hypoglycemic effect.

The occurrence and development of diabetes are related to mitochondrial dysfunction and malfunctioning of the glucose uptake signaling cascade [45, 46]. *In vitro* experiments have shown that compared with free pelargonidin, pelargonidin encapsulated in poly (lactic-co-glycolic acid) (PLGA) produces nanopelargonidin (~12 nm) with an extremely small size. Even when the dose was reduced by 10-fold, the nanopelargonidin showed a greater protective effect of mitochondrial function and the glucose uptake signal cascade, which is expected to be used to prevent diabetes or delay its progression [47]. Similarly, PLGA nanoparticles for curcumin effectively prevent the initiation of inflammation and pancreatic islets/β-cell apoptosis, improve islet β-cell function, and prevent type 1 diabetes mellitus. This formulation increases the oral availability of curcumin by at least 9-fold, improving the curative effects of the diabetic model [48]. Diabetes affects wound healing. Bairagi et al. [49] found that ferulic acid-poly (lactic-co-glycolic acid) (FA-PLGA) nanoparticles not only reduce the levels of blood glucose but local application and oral administration of ferulic acid nanoparticles promote wound healing in diabetic rats better than free ferulic acid.

To enhance the antidiabetic effects of quercetin (Qu), Singh et al. [50] prepared Soluplus ®micellar (SMs) supported on quercetin using the cosolvent evaporation method. Moreover, the *in vitro* release study demonstrated that Qu-SMs sustained release characteristics. Pharmacokinetic studies performed *in vivo* showed that the relative bioavailability of Qu reached 1676% by encapsulating the drug into SMs. To study the efficacy of QU-SMs *in vivo*, diabetic rats induced by streptozotocin were orally administered with QU-SMs and free QU solution. Blood glucose levels in the rats were measured and compared with pure drugs. Qu-SMs-treated animals showed lower blood glucose levels. Therefore, the application of nanocarriers improved the antidiabetes performance of Qu. Oleanolic acid (OA) shows antidiabetic activity against both type 1 and type 2 diabetes. It has been proven that the nanocrystallization of OA improves the bioavailability and pharmacodynamic properties of OA. At the same time, it can enhance the pharmacological efficacy of preventing and treating diabetes and its related metabolic diseases [51].

4.3. Application of Nanodrugs Derived from Natural Products to Treat Neurodegenerative Diseases. So far, nanoparticles have attracted attention for the treatment of psychiatric diseases due to their unique structural advantages, high stability, easy surface functionalization, and modifications, as well as their access across the easy blood-brain barrier (BBB).

4.3.1. Alzheimer's Disease. The biocompatibility and biodegradability of PLGA are recognized but limited by shortcomings of poor water solubility and easy first-pass metabolism of quercetin. Sun et al. [52] prepared PLGA functionalized quercetin nanoparticles (PLGA@QT) to study their effects and safety in treating AD. The prepared nanomedicine shows synergism and detoxification. Most importantly, the effects of PLGA@QT nanoparticles on improving spatial memory increase with increased dose, which is expected to be used in the treatment of AD. Ginsenoside Rg3 has been extensively studied as the main active ingredient of ginseng, and studies have shown its strong antioxidant capacity is beneficial to Alzheimer's disease [53]. To prevent rapid clearance of ginsenoside Rg3 from the blood and increase drug accumulation at the disease site, researchers developed PLGA-Rg3 nanoparticles that can specifically target amyloid plaques/amyloid fibers and determined that PLGA-Rg3 nanoparticles effectively pass through BBB, continuously release ginsenoside Rg3 and reduce the formation of AD plaques. In addition, this nanotherapy results in less side effects and has potential benefits for delaying AD development [54].

Gold nanoparticle-based drug delivery methods have also achieved better intracerebral administration in neurotherapy. This is because gold nanoparticles can easily pass through brain endothelial cells and promote effective drug delivery to the brain [55]. As a result, an anthocyanin-loaded gold nanoparticle coated with PEG used to treat AD was designed, hoping to improve the neuroprotective effects of anthocyanin. It has been confirmed that anthocyanin-loaded PEG-gold nanoparticles have successfully penetrated the brain and showed more significant anti-AD and anti-inflammatory effects compared with anthocyanins alone, with no significant cytotoxic effect son neuronal cells, suggesting that this nanoparticle may be a potential drug for AD treatment [56]. To explore the potential of hesperetin in the treatment of AD and the advantages of nanodrug delivery, Kheradmand et al. [57] used Alzheimer's disease animal models to compare the effects of hesperetin and nanohesperetin on neurobehavioral activity and antioxidant parameters. The experimental results showed that both hesperetin and nanohesperetin improved memory and learning and increased the antioxidation index of the hippocampus. However, it was obvious that nanohesperetin showed better neuroprotective effects than hesperetin and had more therapeutic value.

4.3.2. Parkinson's Disease. In the past few decades, individuals explored the antioxidant properties of flavonoids and discussed their neuroprotective mechanisms. Rutin is a flavonoid that can activate a variety of endogenous antioxidant enzymes and suppress lipid peroxidation, which is considered as a potential drug for the prevention or treatment of PD [58]. Its application is mainly limited to poor water solubility, which leads to less intestinal absorption and low oral availability. Self-nanoemulsifying drug delivery systems are an effective method to improve this defect. Compared with rutin suspension, the optimized formulation increased the relative oral bioavailability of rutin by 2.3-fold. In addition, increased levels of rutin in the brain suggest that self-emulsification improves the permeability of rutin [59]. Schizandrin A (SA) is a promising natural product for anti-Parkinson's disease. It can significantly inhibit SH-SY5Y cytotoxicity induced by 6-hydroxydopamine (6-OHDA) or 1-methyl-4-phenylpyridinium ion (MPP^+) *in vitro*. In zebrafish and PD mouse models, it has significant

protective effects on dopaminergic neuron loss induced by 6-OHDA and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), respectively [60–62]. To increase uptake of SA by the brain and extend the circulation time of SA in the bloodstream, Chen et al. [62] used the flash nanoprecipitation method to encapsulate SA into methoxy poly(ethylene glycol)-block-poly(D,L)-lactic-co-glycolic acid nanoparticles (SA-NPs) with high encapsulation efficiency and high drug loading and is in a sustained release mode. Pharmacokinetic studies showed that SA content in the brain tissue and plasma of rats in the SA-NPs group increased significantly. The SA-NPs exerted strong neuroprotective effects on zebrafish and PD cell models, demonstrating the advantages of the nanodrug in cross-barrier transportation and bioavailability.

4.3.3. Huntington's Disease. Protein misfolding and aggregation into fibrillar deposits are one of the causes of neurodegenerative diseases [63]. It is believed that the abnormal expansion of the polyglutamine (polyQ) repeats in the huntingtin (htt) protein causes mutant huntingtin to form amyloid aggregates, further triggering Huntington's disease (HD) [64]. Trehalose, known as the "sugar of life," is found in many plants, insects, and microorganisms and acts as an important autophagy modulator and antioxidant [65, 66]. The neuroprotective effects of trehalose have been demonstrated in various neurodegeneration models, and the general hypothesis is that trehalose promotes the elimination of protein aggregates by inducing autophagy [67]. Nanosized trehalose has been shown to further enhance this property. Mandal et al. designed a trehalose-functionalized gold nanoparticle that enhanced cell uptake in the form of endocytosis. This improved the inhibitory effects on the aggregation of polyglutamine-containing mutant proteins in neuronal cells [68]. Others synthesized trehalose-functionalized zwitterionic nanoparticles with a size between 20 and 30 nm. Results show that this type of nanotrehalose is safe and efficient and is 1000 times more efficient than molecular trehalose when it comes to inhibiting the accumulation of polyglutamine under extra/intracellular conditions or in HD model mouse brain. In addition, ideal effects could be achieved at the micromolar concentration [69].

In previous studies, curcumin has been reported to show strong antioxidant, anti-inflammatory, and antiprotein aggregation effects, which can improve mitochondrial dysfunction, polyQ-induced compromised neuronal function, cytotoxicity, and cell death [64, 70]. Hickey et al. reported beneficial effects of dietary curcumin on the HD mouse, especially on Huntington aggregates [71]. The most important aspect is that curcumin passes through the BBB making it an ideal neuroprotective compound [72]. However, the clinical application of curcumin is limited due to its poor water solubility, unstable *in vivo* properties, less absorption in the gastrointestinal tract, and rapid metabolism [73, 74]. The nanoparticle drug delivery system protects the stability of curcumin *in vivo* and prevents its enzymatic and PH degradation [75]. Based on these shortcomings of the drug and the advantages of nanoparticles, researchers developed curcumin solid lipid nanoparticles (C-SLN) to enhance oral bioavailability and their neuroprotective effects on HD induced by 3-nitropropionic acid (3-NPD) [76]. The experimental results showed that C-SLN improved the 3-NP-induced oxidative stress by activating the Nrf2 antioxidant pathway. The animal model treated with C-SLN showed reduced mitochondrial swelling, increased cytochrome levels, and improved neuromotor coordination. It is certain that C-SLN has an advantage over curcumin alone.

4.4. Application of Nanodrugs Derived from Natural Products in the Treatment of Cardiovascular Diseases. Cardiovascular diseases (CVD) are recognized as the leading cause of death worldwide [77]. Atherosclerosis and hypertension are risk factors for cardiovascular disease [78]. Many natural products have great potential and bright prospects in the treatment and prevention of cardiovascular diseases, such as curcumin, resveratrol, and epigallocatechin-3-gallate [78].

So far, the development of nanodrugs is mostly focused on tumor-targeted drug delivery and bypassing the BBB to treat brain diseases. The development of nanodrugs related to the treatment of cardiovascular diseases is still in initial stages, especially when it comes to targeted drug delivery. Presently, a variety of nanocarriers such as liposomes, solid lipid nanoparticles, and polymer nanoparticles have been developed to improve the bioavailability of drugs and the targeted treatment of cardiovascular diseases [79]. Therefore, nanotechnology is a promising strategy for the treatment of cardiovascular diseases and has broad application prospects in drug delivery.

The antioxidant and anti-inflammatory properties of resveratrol (Res) and the ability to upregulate endothelial NO synthase (eNOS) have potential beneficial effects on CVD [80]. The low bioavailability and high photosensitivity of the compound are the main issues researchers are trying to overcome with the use of a nanodelivery system.

Lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) (particle sizes between 160-190 nm) can protect resveratrol from degradation and enhance intestinal permeability. SLNs and NLCs can be used for oral administration of resveratrol, which is expected to enhance its efficacy *in vivo* [81]. Epigallocatechin-3-gallate (EGCG) is a powerful natural antioxidant with both hypolipidemic activity and antihypertensive effects. Several studies support the view that EGCG has many benefits in the treatment of cardiovascular diseases [82–84]. However, the low bioavailability and instability of EGCG limit its effectiveness in the prevention and treatment of human cardiovascular diseases. Therefore, the application of nanocarriers can be used as a strategy to enhance its stability and effectiveness [85]. Compared with the same concentration of free EGCG, EGCG conjugated gold nanoparticles showed significant selective affinity and low toxicity to human smooth muscle cells and endothelial cells [86]. The L-Enano (composed of PC, kolliphor HS15, (+)-α-tocopherol acetate, EGCG, and KOdiA-PC), a type of CD36-targeted EGCG-loaded nanoparticles with a particle size of 108 nm that can enhance the stability and sustained release of EGCG, promotes the targeted delivery of EGCG to intimal macrophages, improves the efficacy, and reduces side effects [87].

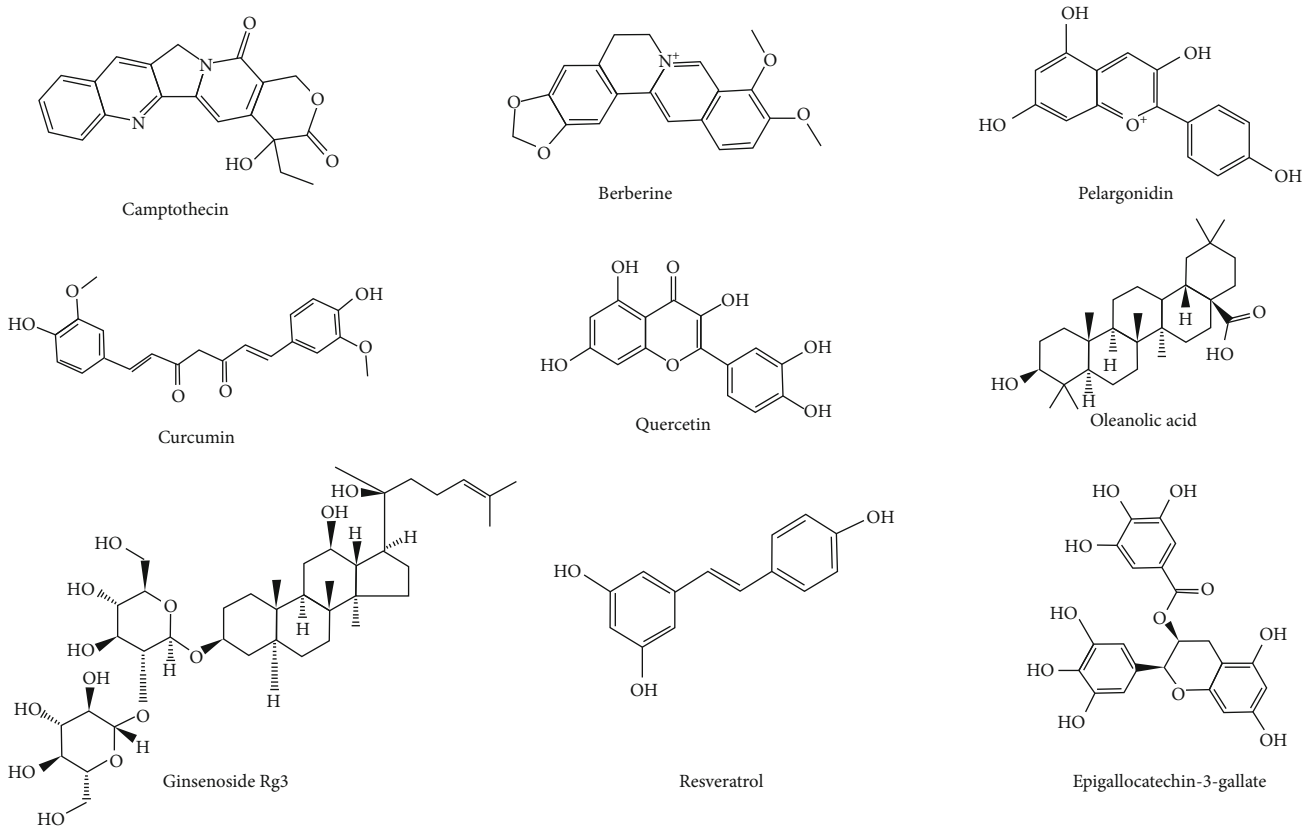

Figure 4: Representative natural product chemical structure.

Hyaluronic acid (HA) is a targeted bioactive molecule associated with inflammation [88]. Thanks to nanotechnology, the uptake efficiency of hyaluronic acid nanoparticles by proinflammatory macrophages *in vitro* is increased by 6-40 times. Hyaluronic acid can target atherosclerotic plaque-associated macrophages in animal models and show strong anti-inflammatory effects. At the same time, hyaluronic acid mediates the targeted delivery of diagnostic agents to specific lesions and performs PET/MRI imaging, which represents a new method for the diagnosis of atherosclerosis [89]. Recombinant high-density lipoprotein (rHDL) can promote cholesterol efflux. Use of HA- (C)-PLGA-rHDL nanoparticles with a particle size of 138 nm enhances cellular cholesterol efflux (2.43 times), and drug loading can achieve a more effective antiatherosclerotic effect [90]. Chitosan is a natural product with strong hypolipidemic activity and shown to have significant benefits in blood lipids and lipoproteins when used alone and is a potential therapeutic agent to reduce the risk of CVD [91, 92]. Due to its good biocompatibility, biodegradability, and nontoxicity, it has become an ideal drug loading system that can improve the bioavailability of anticardiovascular drugs and increase the sustained release of drugs. In short, the combination of these natural product nanocarriers and related disease drugs not only reduces the dose of these drugs but also reduces side effects and achieves stronger therapeutics effects.

5. Conclusions and Future Prospects

The application of nanotechnology in drug delivery has had a positive impact on the treatment of a variety of human diseases. This method is especially essential for the development of appropriate drug delivery methods for hydrophobic drugs that are easily affected by the environment. Researchers are aware of the great potential of pharmacologically active natural products in the prevention and treatment of human diseases and are currently conducting research on natural products. Investigators are trying to use a nanodrug delivery system to improve the limitations of its application and improve efficacy. Nanodrugs containing paclitaxel, camptothecin, curcumin, or resveratrol have been on the market or are used in clinical research, showing very promising results. Some polysaccharide natural products show nice pharmacological activities and can be used as excellent nanocarrier materials, which highlight the advantages and potential of natural products in the nanodrug field. So far, results of natural product-based nanopreparations in animal models show better stability and sustained release ability, as well as exhibit ideal therapeutics effects at low doses. In turn, this increases the safety of long-term use of this system (Figure 4).

However, the clinical transformation of these nanodrugs is still a challenge. One of the main reasons may be inconsistencies between the occurrence and development of human

and animal diseases. Long-term treatment of diseases is inevitable, which requires that designed nanodrugs must meet many criteria, such as stability in systemic circulation and release effective concentrations of drugs in the desired areas without affecting healthy tissues. It is worth noting that nanoparticles that deliver drugs can stimulate or inhibit the immune response and may remain in the body, which requires researchers to design appropriate nanodrugs and modify according to disease characteristics and drugs and carry out extensive immunotoxicology research before translating to the clinical. In the future, it is necessary to establish a complete clinical evaluation and detection system to achieve the transition from basic to clinical research.

In summary, we have entered a nanomedicine era of natural products. Even though there is still some way to go before this system is truly optimized, it is obvious that nanodrugs based on natural products show broad application prospects in modern medicine.

Data Availability

No data were used to support this study.

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

[1] D. J. Newman and G. M. Cragg, "Natural products as sources of new drugs from 1981 to 2014," *Journal of Natural Products*, vol. 79, no. 3, pp. 629–661, 2016.

[2] F. E. Koehn and G. T. Carter, "The evolving role of natural products in drug discovery," *Nature Reviews. Drug Discovery*, vol. 4, no. 3, pp. 206–220, 2005.

[3] M. Feher and J. M. Schmidt, "Property distributions: differences between drugs, natural products, and molecules from combinatorial chemistry," *Journal of Chemical Information and Computer Sciences*, vol. 43, no. 1, pp. 218–227, 2003.

[4] A. R. Bilia, V. Piazzini, C. Guccione et al., "Improving on nature: the role of nanomedicine in the development of clinical natural drugs," *Planta Medica*, vol. 83, no. 5, pp. 366–381, 2017.

[5] B. David, J.-L. Wolfender, and D. A. Dias, "The pharmaceutical industry and natural products: historical status and new trends," *Phytochemistry Reviews*, vol. 14, pp. 299–315, 2015.

[6] R. Watkins, L. Wu, C. Zhang, R. M. Davis, and B. Xu, "Natural product-based nanomedicine: recent advances and issues," *International Journal of Nanomedicine*, vol. 10, pp. 6055–6074, 2015.

[7] Q. Liu, A. J. Lawrence, and J. H. Liang, "Traditional Chinese medicine for treatment of alcoholism: from ancient to modern," *The American Journal of Chinese Medicine*, vol. 39, no. 1, pp. 1–13, 2011.

[8] M. Ernst, O. M. Grace, C. H. Saslis-Lagoudakis, N. Nilsson, H. T. Simonsen, and N. Rønsted, "Global medicinal uses of Euphorbia L. (Euphorbiaceae)," *Journal of Ethnopharmacology*, vol. 176, pp. 90–101, 2015.

[9] P. Mannangatti and K. N. Naidu, "Indian herbs for the treatment of neurodegenerative disease," *Advances in Neurobiology*, vol. 12, pp. 323–336, 2016.

[10] P. Kumari, S. Luqman, and A. Meena, "Application of the combinatorial approaches of medicinal and aromatic plants with nanotechnology and its impacts on healthcare," *Daru*, vol. 27, no. 1, pp. 475–489, 2019.

[11] V. L. Challinor and H. B. Bode, "Bioactive natural products from novel microbial sources," *Annals of the New York Academy of Sciences*, vol. 1354, no. 1, pp. 82–97, 2015.

[12] G. D. Wright, "Opportunities for natural products in 21stcentury antibiotic discovery," *Natural Product Reports*, vol. 34, no. 7, pp. 694–701, 2017.

[13] A. L. Demain, "Importance of microbial natural products and the need to revitalize their discovery," *Journal of Industrial Microbiology & Biotechnology*, vol. 41, no. 2, pp. 185–201, 2014.

[14] B. Haefner, "Drugs from the deep: marine natural products as drug candidates," *Drug Discovery Today*, vol. 8, no. 12, pp. 536–544, 2003.

[15] P. V. Snelgrove, "An ocean of discovery: biodiversity beyond the census of marine life," *Planta Medica*, vol. 82, no. 9-10, pp. 790–799, 2016.

[16] S. A. M. Khalifa, N. Elias, M. A. Farag et al., "Marine natural products: a source of novel anticancer drugs," *Marine Drugs*, vol. 17, no. 9, p. 491, 2019.

[17] R. C. F. Cheung, T. B. Ng, J. H. Wong, Y. Chen, and W. Y. Chan, "Marine natural products with anti-inflammatory activity," *Applied Microbiology and Biotechnology*, vol. 100, no. 4, pp. 1645–1666, 2016.

[18] S. Sagar, M. Kaur, and K. P. Minneman, "Antiviral lead compounds from marine sponges," *Marine Drugs*, vol. 8, no. 10, pp. 2619–2638, 2010.

[19] D. J. Faulkner, "Marine natural products (1999)," *Natural Product Reports*, vol. 18, no. 1, pp. 1–49, 2001.

[20] E. M. el-Hossary, C. Cheng, M. M. Hamed et al., "Antifungal potential of marine natural products," *European Journal of Medicinal Chemistry*, vol. 126, pp. 631–651, 2017.

[21] D. X. Kong, Y. Y. Jiang, and H. Y. Zhang, "Marine natural products as sources of novel scaffolds: achievement and concern," *Drug Discovery Today*, vol. 15, no. 21-22, pp. 884–886, 2010.

[22] P. Zahedi, R. Yoganathan, M. Piquette-Miller, and C. Allen, "Recent advances in drug delivery strategies for treatment of ovarian cancer," *Expert Opinion on Drug Delivery*, vol. 9, no. 5, pp. 567–583, 2012.

[23] V. Agrahari, P. A. Burnouf, T. Burnouf, and V. Agrahari, "Nanoformulation properties, characterization, and behavior in complex biological matrices: challenges and opportunities

for brain-targeted drug delivery applications and enhanced translational potential," *Advanced Drug Delivery Reviews*, vol. 148, pp. 146–180, 2019.

[24] J. M. Andrade, L. Custódio, A. Romagnoli et al., "Antitubercular and anti-inflammatory properties screening of natural products from Plectranthus species," *Future Medicinal Chemistry*, vol. 10, no. 14, pp. 1677–1691, 2018.

[25] S. Pinteus, J. Silva, C. Alves, A. Horta, O. Thomas, and R. Pedrosa, "Antioxidant and cytoprotective activities of Fucus spiralis seaweed on a human cell in vitro model," *International Journal of Molecular Sciences*, vol. 18, no. 2, p. 292, 2017.

[26] P. Tewary, A. A. Gunatilaka, and T. J. Sayers, "Using natural products to promote caspase-8-dependent cancer cell death," *Cancer immunology, immunotherapy : CII*, vol. 66, no. 2, pp. 223–231, 2017.

[27] F. Bray, A. Jemal, N. Grey, J. Ferlay, and D. Forman, "Global cancer transitions according to the Human Development Index (2008-2030): a population-based study," *The Lancet Oncology*, vol. 13, no. 8, pp. 790–801, 2012.

[28] F. Bray, J. Ferlay, I. Soerjomataram, R. L. Siegel, L. A. Torre, and A. Jemal, "Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries," *CA: a Cancer Journal for Clinicians*, vol. 68, no. 6, pp. 394–424, 2018.

[29] E. Tahover, A. Hubert, M. Temper et al., "An observational cohort study of bevacizumab and chemotherapy in metastatic colorectal cancer patients: safety and efficacy with analysis by age group," *Targeted Oncology*, vol. 10, no. 1, pp. 55–63, 2015.

[30] S. Dutta, S. Mahalanobish, S. Saha, S. Ghosh, and P. C. Sil, "Natural products: an upcoming therapeutic approach to cancer," *Food and Chemical Toxicology*, vol. 128, pp. 240–255, 2019.

[31] N. Liu, H. Huang, S. Liu et al., "Calcium channel blocker verapamil accelerates gambogic acid-induced cytotoxicity _via_ enhancing proteasome inhibition and ROS generation," *Toxicology In Vitro*, vol. 28, no. 3, pp. 419–425, 2014.

[32] L. Ouyang, Y. Luo, M. Tian et al., "Plant natural products: from traditional compounds to new emerging drugs in cancer therapy," *Cell Proliferation*, vol. 47, no. 6, pp. 506–515, 2014.

[33] R. Yuan, Y. Hou, W. Sun et al., "Natural products to prevent drug resistance in cancer chemotherapy: a review," *Annals of the New York Academy of Sciences*, vol. 1401, no. 1, pp. 19–27, 2017.

[34] B. N. Ho, C. M. Pfeffer, and A. T. K. Singh, "Update on nanotechnology-based drug delivery systems in cancer treatment," *Anticancer Research*, vol. 37, no. 11, pp. 5975–5981, 2017.

[35] E. Martino, S. Della Volpe, E. Terribile et al., "The long story of camptothecin: from traditional medicine to drugs," *Bioorganic & Medicinal Chemistry Letters*, vol. 27, no. 4, pp. 701–707, 2017.

[36] Y. Wen, Y. Wang, X. Liu et al., "Camptothecin-based nanodrug delivery systems," *Cancer Biology & Medicine*, vol. 14, no. 4, pp. 363–370, 2017.

[37] S. Gaur, Y. Wang, L. Kretzner et al., "Pharmacodynamic and pharmacogenomic study of the nanoparticle conjugate of camptothecin CRLX101 for the treatment of cancer," *Nanomedicine*, vol. 10, no. 7, pp. 1477–1486, 2014.

[38] G. J. Weiss, J. Chao, J. D. Neidhart et al., "First-in-human phase 1/2a trial of CRLX101, a cyclodextrin-containing polymer-camptothecin nanopharmaceutical in patients with advanced solid tumor malignancies," *Investigational New Drugs*, vol. 31, no. 4, pp. 986–1000, 2013.

[39] Y. Zhao, F. Chen, Y. Pan et al., "Nanodrug formed by coassembly of dual anticancer drugs to inhibit cancer cell drug resistance," *ACS Applied Materials & Interfaces*, vol. 7, no. 34, pp. 19295–19305, 2015.

[40] M. Y. Peng, S. Y. Qin, H. Z. Jia, D. Zheng, L. Rong, and X. Zhang, "Self-delivery of a peptide-based prodrug for tumor-targeting therapy," *Nano Research*, vol. 9, no. 3, pp. 663–673, 2016.

[41] J. Li, L. Yang, R. Shen et al., "Self-nanoemulsifying system improves oral absorption and enhances anti-acute myeloid leukemia activity of berberine," *J Nanobiotechnology*, vol. 16, no. 1, p. 76, 2018.

[42] L. Jiang, Y. Wang, Q. Yin et al., "Phycocyanin: a potential drug for cancer treatment," *Journal Of Cancer*, vol. 8, no. 17, pp. 3416–3429, 2017.

[43] P. Yang, B. Li, Q. F. Yin, and Y. J. Wang, "Carboxymethyl chitosan nanoparticles coupled with CD59-specific ligand peptide for targeted delivery of C-phycocyanin to HeLa cells," *Tumour Biology*, vol. 39, 2017.

[44] W. Tai, R. Mo, J. di et al., "Bio-inspired synthetic nanovesicles for glucose-responsive release of insulin," *Biomacromolecules*, vol. 15, no. 10, pp. 3495–3502, 2014.

[45] A. Samadder, S. Das, J. Das, and A. R. Khuda-Bukhsh, "Relative efficacies of insulin and poly (lactic-co-glycolic) acid encapsulated nano-insulin in modulating certain significant biomarkers in arsenic intoxicated L6 cells," *B, Biointerfaces*, vol. 109, pp. 10–19, 2013.

[46] A. Samadder, J. Das, S. Das et al., "Poly(lactic-co-glycolic) acid loaded nano-insulin has greater potentials of combating arsenic induced hyperglycemia in mice: some novel findings," *Toxicology and Applied Pharmacology*, vol. 267, no. 1, pp. 57–73, 2013.

[47] A. Samadder, D. Tarafdar, S. K. Abraham, K. Ghosh, and A. R. Khuda-Bukhsh, "Nano-pelargonidin protects hyperglycemic-induced L6 cells against mitochondrial dysfunction," *Planta Medica*, vol. 83, no. 5, pp. 468–475, 2017.

[48] R. Ganugula, M. Arora, P. Jaisamut et al., "Nano-curcumin safely prevents streptozotocin-induced inflammation and apoptosis in pancreatic beta cells for effective management of type 1 diabetes mellitus," *British Journal of Pharmacology*, vol. 174, no. 13, pp. 2074–2084, 2017.

[49] U. Bairagi, P. Mittal, J. Singh, and B. Mishra, "Preparation, characterization, and in vivo evaluation of nano formulations of ferulic acid in diabetic wound healing," *Drug Development and Industrial Pharmacy*, vol. 44, no. 11, pp. 1783–1796, 2018.

[50] J. Singh, P. Mittal, G. Vasant Bonde, G. Ajmal, and B. Mishra, "Design, optimization, characterization and in-vivo evaluation of quercetin enveloped Soluplus®/P407 micelles in diabetes treatment," *Artificial Cells, Nanomedicine, and Biotechnology*, vol. 46, supplement 3, pp. S546–S555, 2018.

[51] S. Wang, L. B. du, L. Jin et al., "Nano-oleanolic acid alleviates metabolic dysfunctions in rats with high fat and fructose diet," *Biomedicine & Pharmacotherapy*, vol. 108, pp. 1181–1187, 2018.

[52] D. Sun, N. Li, W. Zhang et al., "Design of PLGA-functionalized quercetin nanoparticles for potential use in Alzheimer's disease," *Colloids and Surfaces. B, Biointerfaces*, vol. 148, pp. 116–129, 2016.

[53] Y. Zhang, X. Yang, S. Wang, and S. Song, "Ginsenoside Rg3 prevents cognitive impairment by improving mitochondrial dysfunction in the rat model of Alzheimer's disease," *Journal of Agricultural and Food Chemistry*, vol. 67, no. 36, pp. 10048–10058, 2019.

[54] R. Aalinkeel, H. L. Kutscher, A. Singh et al., "Neuroprotective effects of a biodegradable poly(lactic-co-glycolic acid)-ginsenoside Rg3 nanoformulation: a potential nanotherapy for Alzheimer's disease?," *Journal of Drug Targeting*, vol. 26, no. 2, pp. 182–193, 2018.

[55] D. Male, R. Gromnicova, and C. McQuaid, "Gold nanoparticles for imaging and drug transport to the CNS," *International Review of Neurobiology*, vol. 130, pp. 155–198, 2016.

[56] M. J. Kim, S. U. Rehman, F. U. Amin, and M. O. Kim, "Enhanced neuroprotection of anthocyanin-loaded PEG-gold nanoparticles against A$\beta_{1\text{-}42}$-induced neuroinflammation and neurodegeneration _via_ the NF-$_K$B /JNK/GSK3 β signaling pathway," *Nanomedicine*, vol. 13, no. 8, pp. 2533–2544, 2017.

[57] E. Kheradmand, A. Hajizadeh Moghaddam, and M. Zare, "Neuroprotective effect of hesperetin and nano-hesperetin on recognition memory impairment and the elevated oxygen stress in rat model of Alzheimer's disease," *Biomedicine & Pharmacotherapy*, vol. 97, pp. 1096–1101, 2018.

[58] K. B. Magalingam, A. K. Radhakrishnan, and N. Haleagrahara, "Protective mechanisms of flavonoids in Parkinson's disease," *Oxidative Medicine and Cellular Longevity*, vol. 2015, Article ID 314560, 2015.

[59] S. Sharma, J. K. Narang, J. Ali, and S. Baboota, "Synergistic antioxidant action of vitamin E and rutin SNEDDS in ameliorating oxidative stress in a Parkinson's disease model," *Nanotechnology*, vol. 27, no. 37, article 375101, 2016.

[60] F. Sa, L. Q. Zhang, C. M. Chong et al., "Discovery of novel antiparkinsonian effect of schisantherin A in _in vitro_ and _in vivo_," *Neuroscience Letters*, vol. 593, pp. 7–12, 2015.

[61] L. Q. Zhang, F. Sa, C. M. Chong et al., "Schisantherin A protects against 6-OHDA-induced dopaminergic neuron damage in zebrafish and cytotoxicity in SH-SY5Y cells through the ROS/NO and AKT/GSK3β pathways," *Journal of Ethnopharmacology*, vol. 170, pp. 8–15, 2015.

[62] T. Chen, C. Li, Y. Li et al., "Small-sized mPEG-PLGA nanoparticles of schisantherin A with sustained release for enhanced brain uptake and anti-Parkinsonian activity," *Applied Materials & Interfaces*, vol. 9, no. 11, pp. 9516–9527, 2017.

[63] Z. Dhouafli, K. Cuanalo-Contreras, E. A. Hayouni, C. E. Mays, C. Soto, and I. Moreno-Gonzalez, "Inhibition of protein misfolding and aggregation by natural phenolic compounds," *Cellular and Molecular Life Sciences*, vol. 75, no. 19, pp. 3521–3538, 2018.

[64] A. Chongtham and N. Agrawal, "Curcumin modulates cell death and is protective in Huntington's disease model," *Scientific Reports*, vol. 6, no. 1, 2016.

[65] K. Hosseinpour-Moghaddam, M. Caraglia, and A. Sahebkar, "Autophagy induction by trehalose: molecular mechanisms and therapeutic impacts," *Journal of Cellular Physiology*, vol. 233, no. 9, pp. 6524–6543, 2018.

[66] Y. Mizunoe, M. Kobayashi, Y. Sudo et al., "Trehalose protects against oxidative stress by regulating the Keap1-Nrf2 and autophagy pathways," *Redox Biology*, vol. 15, pp. 115–124, 2018.

[67] H. J. Lee, Y. S. Yoon, and S. J. Lee, "Mechanism of neuroprotection by trehalose: controversy surrounding autophagy induction," *Cell Death & Disease*, vol. 9, no. 7, p. 712, 2018.

[68] S. Mandal, K. Debnath, N. R. Jana, and N. R. Jana, "Trehalose-functionalized gold nanoparticle for inhibiting intracellular protein aggregation," *Langmuir*, vol. 33, no. 49, pp. 13996–14003, 2017.

[69] K. Debnath, N. Pradhan, B. K. Singh, N. R. Jana, and N. R. Jana, "Poly(trehalose) nanoparticles prevent amyloid aggregation and suppress polyglutamine aggregation in a Huntington's disease model mouse," *Applied Materials & Interfaces*, vol. 9, no. 28, pp. 24126–24139, 2017.

[70] F. Ullah, A. Liang, A. Rangel, E. Gyengesi, G. Niedermayer, and G. Münch, "High bioavailability curcumin: an anti-inflammatory and neurosupportive bioactive nutrient for neurodegenerative diseases characterized by chronic neuroinflammation," *Archives of Toxicology*, vol. 91, no. 4, pp. 1623–1634, 2017.

[71] M. A. Hickey, C. Zhu, V. Medvedeva et al., "Improvement of neuropathology and transcriptional deficits in CAG 140 knock-in mice supports a beneficial effect of dietary curcumin in Huntington's disease," *Molecular Neurodegeneration*, vol. 7, no. 1, 2012.

[72] H. Yavarpour-Bali, M. Ghasemi-Kasman, and M. Pirzadeh, "Curcumin-loaded nanoparticles: a novel therapeutic strategy in treatment of central nervous system disorders," *International Journal of Nanomedicine*, vol. Volume 14, pp. 4449–4460, 2019.

[73] G. Mazzanti and S. Di Giacomo, "Curcumin and resveratrol in the management of cognitive disorders: what is the clinical evidence?," *Molecules*, vol. 21, no. 9, p. 1243, 2016.

[74] M. M. Serafini, M. Catanzaro, M. Rosini, M. Racchi, and C. Lanni, "Curcumin in Alzheimer's disease: can we think to new strategies and perspectives for this molecule?," *Pharmacological Research*, vol. 124, pp. 146–155, 2017.

[75] M. Szymusiak, X. Hu, P. A. Leon Plata, P. Ciupinski, Z. J. Wang, and Y. Liu, "Bioavailability of curcumin and curcumin glucuronide in the central nervous system of mice after oral delivery of nano-curcumin," *International Journal of Pharmaceutics*, vol. 511, no. 1, pp. 415–423, 2016.

[76] R. Sandhir, A. Yadav, A. Mehrotra, A. Sunkaria, A. Singh, and S. Sharma, "Curcumin nanoparticles attenuate neurochemical and neurobehavioral deficits in experimental model of Huntington's disease," *Neuromolecular Medicine*, vol. 16, no. 1, pp. 106–118, 2014.

[77] C. Caballero-George, "Cardiovascular protection by natural products," *Planta Medica*, vol. 81, p. 623, 2015.

[78] B. Waltenberger, A. Mocan, K. Šmejkal, E. Heiss, and A. Atanasov, "Natural products to counteract the epidemic of cardiovascular and metabolic disorders," *Molecules*, vol. 21, no. 6, p. 807, 2016.

[79] P. Gupta, E. Garcia, A. Sarkar et al., "Nanoparticle based treatment for cardiovascular diseases," *Cardiovascular & Hematological Disorders Drug Targets*, vol. 19, no. 1, pp. 33–44, 2019.

[80] D. Bonnefont-Rousselot, "Resveratrol and cardiovascular diseases," *Nutrients*, vol. 8, no. 5, p. 250, 2016.

[81] A. R. Neves, S. Martins, M. A. Segundo, and S. Reis, "Nanoscale delivery of resveratrol towards enhancement of supplements and nutraceuticals," *Nutrients*, vol. 8, no. 3, p. 131, 2016.

[82] Q. Y. Eng, P. V. Thanikachalam, and S. Ramamurthy, "Molecular understanding of epigallocatechin gallate (EGCG) in cardiovascular and metabolic diseases," *Journal of Ethnopharmacology*, vol. 210, pp. 296–310, 2018.

[83] B. J. Qian, C. C. Tian, X. H. Ling et al., "miRNA-150-5p associate with antihypertensive effect of epigallocatechin-3-gallate revealed by aorta miRNome analysis of spontaneously hypertensive rat," *Life Sciences*, vol. 203, pp. 193–202, 2018.

[84] S. Y. Cao, C. N. Zhao, R. Y. Gan et al., "Effects and mechanisms of tea and its bioactive compounds for the prevention and treatment of cardiovascular diseases: an updated review," *Antioxidants*, vol. 8, 2019.

[85] A. Granja, I. Frias, A. R. Neves, M. Pinheiro, and S. Reis, "Therapeutic potential of epigallocatechin gallate nanodelivery systems," *BioMed Research International*, vol. 2017, 2017.

[86] M. Khoobchandani, K. Katti, A. Maxwell, W. Fay, and K. Katti, "Laminin receptor-avid nanotherapeutic EGCg-AuNPs as a potential alternative therapeutic approach to prevent restenosis," *International Journal of Molecular Sciences*, vol. 17, no. 3, p. 316, 2016.

[87] J. Zhang, S. Nie, R. Martinez-Zaguilan, S. R. Sennoune, and S. Wang, "Formulation, characteristics and antiatherogenic bioactivities of CD36-targeted epigallocatechin gallate (EGCG)-loaded nanoparticles," *The Journal of Nutritional Biochemistry*, vol. 30, pp. 14–23, 2016.

[88] P. N. Sudha and M. H. Rose, "Beneficial effects of hyaluronic acid," *Advances in Food and Nutrition Research*, vol. 72, pp. 137–176, 2014.

[89] T. J. Beldman, M. L. Senders, A. Alaarg et al., "Hyaluronan nanoparticles selectively target plaque-associated macrophages and improve plaque stability in atherosclerosis," *ACS Nano*, vol. 11, no. 6, pp. 5785–5799, 2017.

[90] M. Zhang, J. He, C. Jiang et al., "Plaque-hyaluronidase-responsive high-density-lipoprotein-mimetic nanoparticles for multistage intimal-macrophage-targeted drug delivery and enhanced anti-atherosclerotic therapy," *International Journal of Nanomedicine*, vol. Volume 12, pp. 533–558, 2017.

[91] M. Rizzo, R. V. Giglio, D. Nikolic et al., "Effects of chitosan on plasma lipids and lipoproteins: a 4-month prospective pilot study," *Angiology*, vol. 65, no. 6, pp. 538–542, 2014.

[92] A. M. Patti, N. Katsiki, D. Nikolic, K. al-Rasadi, and M. Rizzo, "Nutraceuticals in lipid-lowering Treatment," *Angiology*, vol. 66, no. 5, pp. 416–421, 2015.