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The Potential of Ursolic Acid Nanoformulations As Drug Delivery Systems in Alzheimer's Disease Therapy and Research

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Abstract: Scientific studies have demonstrated that Nanoparticles have become a promising contributor towards Alzheimer's disease (AD) research prospects offering significant advantages in imaging diagnostics as well as therapy. These particles offer better prospects in terms of solubility, permeability and bioavailability due to their nanoscale size which enables effective drug delivery to particular brain areas while reducing off-target side-effects. Ursolic acid (UA), a bioactive compound with promising therapeutic properties, faces challenges in clinical applications due to its poor solubility and low bioavailability. To address these limitations, UA was encapsulated using three different polymer-based nanoparticle formulations: Gum Acacia (UGNPs), Eudragit (UE-NPs), and Gum Ghatti (UAGG-NPs). This study compares the physicochemical properties, drug loading efficiency, release profiles, and antioxidant activities of these UA-loaded nanoparticles. All formulations demonstrated effective encapsulation and sustained drug release, with notable variations in stability, antioxidant activity, and enzyme inhibition. The findings suggest that polymer-based nanoparticles significantly enhance UA's therapeutic potential, with each formulation exhibiting distinct advantages.

Further analysis unravels the comparative benefits of these delivery systems, highlighting their implications for oxidative stress-related and neurodegenerative disorders. UA-Nps demonstrated strong acetylcholinesterase (AChE) inhibition, suggesting a potential role in neurodegenerative disease therapy. This comparative analysis highlights the advantages of Eudragit-based nanoparticles for enhanced UA delivery while also recognizing the therapeutic potential of Gum Acacia and Gum Ghatti formulations. The safety, effectiveness and long-term consequences of nanotechnology-based UA formulation for AD treatment and management require further clinical research. The initial step in the same direction has been taken throughout this investigation and analysis.

Keywords: Drug Delivery, Nano biomedicine, Alzheimer's Disease, Ursolic Acid

I. Introduction

Neurodegenerative diseases, including Alzheimer's disease (AD) and various forms of dementia, pose significant healthcare challenges due to their progressive nature and lack of effective treatments. AD is characterized by hallmark pathological features such as amyloid-beta (Aβ) aggregation, tau protein hyperphosphorylation, oxidative stress, and neuroinflammation. Oxidative stress plays a crucial role in neuronal dysfunction and apoptosis, contributing to cognitive decline. Emerging evidence suggests that nanoparticle-based drug delivery can enhance the bioavailability of neuroprotective agents like Ursolic Acid and facilitate their passage across the BBB [1]. By leveraging nanotechnology, it is possible to improve UA's therapeutic efficacy and target key pathogenic mechanisms of AD and other neurodegenerative disorders.

Ursolic acid (UA), a pentacyclic triterpenoid found in various medicinal plants, is well-documented for its anti-inflammatory, antioxidant, and anticancer properties. It exerts neuroprotective effects by modulating oxidative stress, reducing neuroinflammation, and inhibiting key molecular pathways involved in neurodegeneration. UA's ability to scavenge free radicals, suppress pro-inflammatory cytokines, and regulate apoptotic mechanisms makes it a strong candidate for treating conditions characterized by oxidative damage and chronic inflammation. Additionally, UA has been reported to inhibit cancer cell proliferation by inducing apoptosis and autophagy while exerting protective effects against cardiovascular and metabolic disorders [2]. Despite these therapeutic benefits, the clinical application of UA remains limited due to its hydrophobic nature and poor bioavailability. To overcome UA's solubility and bioavailability challenges, polymer-based nanoparticles offer a promising approach for drug encapsulation and controlled release. UA, chemically is shown in figure 1

Figure 1.

The structure of Ursolic Acid is depicted. A pentacyclic triterpenoid, Ursolic Acid (UA) has the molecular formula $C_{30}H_{48}O_3$. Five interwoven rings (A B C D and E) form its structure in a fused pattern resembling the ursane skeleton. It contains numerous methyl groups a carboxyl (-COOH) group at C28 and a hydroxyl (-OH) group at C3. Increased membrane permeability due to this lipophilic structure supports its pharmacological actions including anti-inflammatory, anti-cancer and neuroprotective effects as well as its bioavailability.

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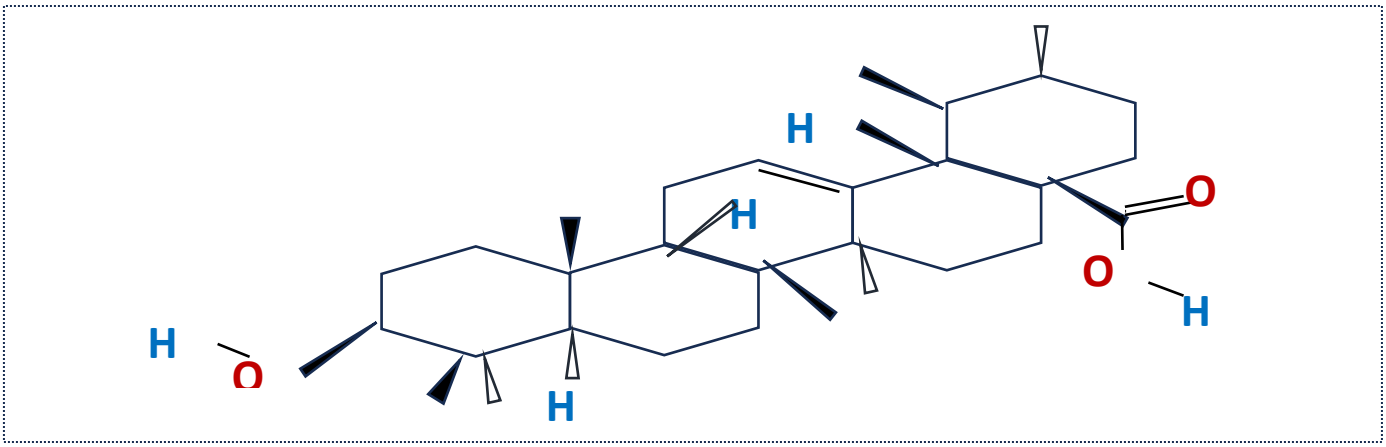

Nanotechnology has revolutionized drug delivery by enabling precise targeting, improved solubility, and controlled release of therapeutic agents. Nanoparticle-based drug delivery systems are particularly valuable in enhancing the pharmacokinetic and pharmacodynamic profiles of bioactive compounds with poor solubility and low bioavailability. Among these, polymeric, lipid-based, and metal nanoparticles have emerged as promising platforms for transporting therapeutic molecules across physiological barriers, including the blood-brain barrier (BBB). Key challenges in current AD treatments are shown in figure 2 and figure 3 shows potential of nanoformulations in AD therapy.

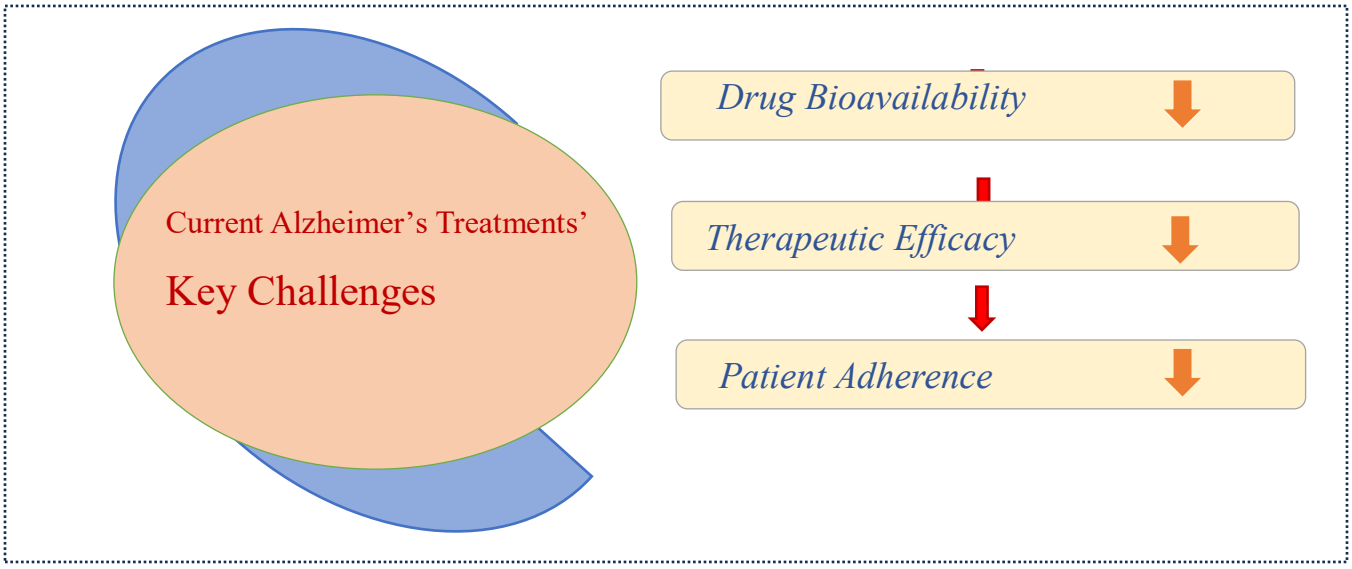

Figure 2. Key challenges in currently prevalent Alzheimer's disease treatments and therapies; Limited bioavailability of administered drug, Low therapeutic efficacy, and Limited patient adherence

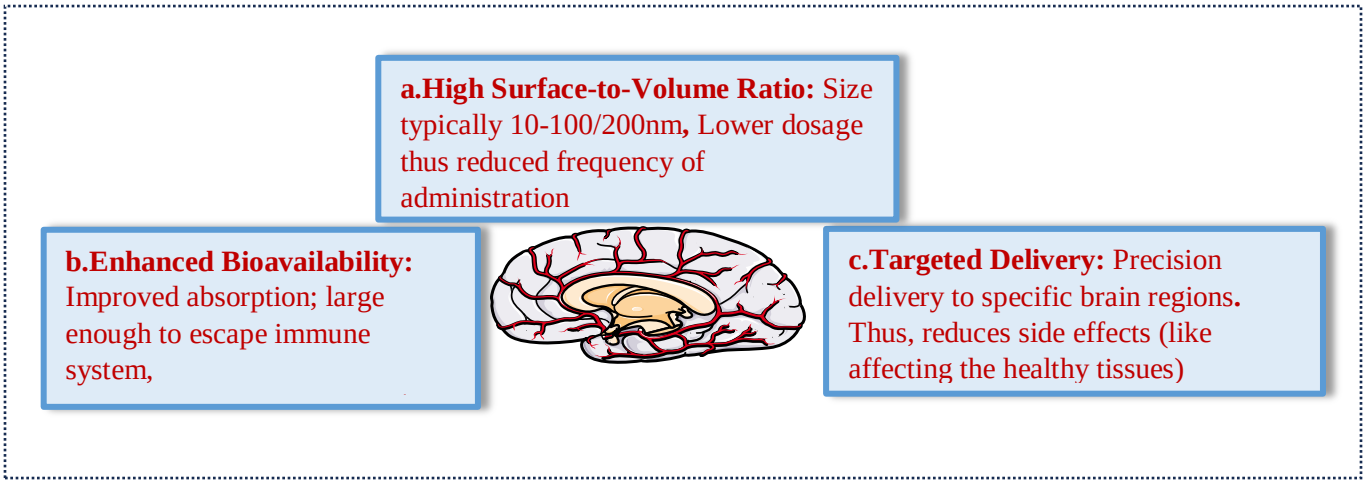

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Figure 3. Potential of nanoformulations in Alzheimer's Disease therapy. Illustration of three major advantages of nanoformulations based drugs against neurodegeneration over other traditional drug delivery systems; module a) depicts the advantage of high surface-to-volume ratio, module b) depicts enhanced bioavailability of nanoformulations based drugs, and module c) discusses targeted delivery of the nanoparticulate systems. Nanoparticles offer unique advantages in the diagnosis, imaging, and treatment of Alzheimer's disease due to their size, surface properties, and ability to interact with biological systems.

Polymeric nanoparticles, in particular, offer advantages such as biocompatibility, tenable drug release, and stability, making them ideal carriers for neuroprotective agents. Advanced formulations, including solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), dendrimers, and polymeric micelles, have shown efficacy in delivering drugs for neurodegenerative diseases, cancer therapy, and inflammatory disorders [3].

In this study, three different polymer matrices; Gum Acacia (GA), Eudragit (EU), and Gum Ghatti (GG) were employed to formulate UA-loaded nanoparticles. These polymers were selected for their biocompatibility, drug-carrying capabilities, and stability in biological environments. Gum Acacia is a natural polysaccharide known for its emulsifying and stabilizing properties, making it a suitable carrier for hydrophobic drugs. Eudragit, a synthetic copolymer, has been widely used in pharmaceutical formulations for controlled drug release due to its pH-dependent solubility. Gum Ghatti, another natural polysaccharide, possesses excellent film-forming and stabilizing properties, offering potential advantages in sustained drug release applications [4].

This study aims to compare the efficiency of UA delivery using these three polymer-based nanoparticle formulations by evaluating their physicochemical properties, drug loading efficiency, release kinetics, and therapeutic potential. By harnessing nanotechnology and polymeric carriers, this research seeks to improve UA's pharmacological effectiveness, particularly for oxidative stress-related diseases such as AD, dementia, and cancer. The findings of this study will contribute to the ongoing development of nanomedicine strategies for neurodegenerative and inflammatory disorders, paving the way for more effective therapeutic interventions.

II. Materials and Methods

Three types of UA-loaded nanoparticles were prepared:

Gum Acacia Nanoparticles (UGNPs) were synthesized using ionic gelation, optimizing encapsulation efficiency through UA's hydrophobic interaction with Gum Acacia.

Eudragit Nanoparticles (UE-NPs) were formulated using the solvent evaporation method, targeting improved stability and controlled drug release.

Gum Ghatti Nanoparticles (UAGG-NPs) were prepared via nanoprecipitation, leveraging Gum Ghatti's stabilizing properties for enhanced bioavailability.

Nanoparticle characterization included particle size analysis (PSA), zeta potential, morphological studies via SEM/TEM, FTIR for molecular interactions, and TGA for thermal stability. Drug loading efficiency and encapsulation efficiency were also evaluated. Antioxidant activity was assessed using DPPH and ABTS assays, while drug release profiles were determined through in-vitro release studies.

Preparation of UA-Loaded Nanoparticles

Synthesis of Gum Acacia Nanoparticles (UGNPs): UGNPs were synthesized using the ionic gelation method, optimizing encapsulation efficiency by leveraging the hydrophobic interactions between UA and Gum Acacia. Ursolic acid (UA), Gum Acacia, sodium tripolyphosphate (TPP), ethanol, and deionized water were used as materials. UA (10 mg) was dissolved in 5 mL of ethanol. Gum Acacia (100 mg) was dispersed in 50 mL of deionized water and stirred for 2 hours. The UA solution was added dropwise to the Gum Acacia dispersion under constant magnetic stirring (600 rpm) at room temperature. TPP (0.1% w/v) was added to crosslink the nanoparticles, stabilizing them. The nanoparticle suspension was centrifuged at 12,000 rpm for 30 min and washed twice with deionized water. The final product was lyophilized and stored at 4°C for further analysis.

Synthesis of Eudragit Nanoparticles (UE-NPs): UE-NPs were prepared using the solvent evaporation method, ensuring improved stability and sustained release. UA, Eudragit RL100, acetone, polyvinyl alcohol (PVA), and deionized water were used as materials. UA (10 mg) and Eudragit RL100 (100 mg) were dissolved in 10 mL of acetone. The organic phase was added dropwise to 50 mL of aqueous PVA solution (0.5% w/v) under continuous stirring at 1000 rpm. The mixture was stirred for 3 hours until complete evaporation of acetone. The nanoparticles were collected by centrifugation at 15,000 rpm for 20 min and washed with deionized water. The final UE-NPs were lyophilized and stored at 4°C.

Synthesis of Gum Ghatti Nanoparticles (UAGG-NPs): UAGG-NPs were formulated using the nanoprecipitation technique, enhancing bioavailability. UA, Gum Ghatti, ethanol, and deionized water were used as materials. UA (10 mg) was dissolved in 5 mL of ethanol. Gum Ghatti (100 mg) was dissolved in 50 mL of deionized water under constant stirring. The UA solution was added dropwise to the aqueous phase under continuous stirring at 800 rpm. The mixture was left stirring for 3 hours to allow complete nanoprecipitation. Nanoparticles were collected via centrifugation at 10,000 rpm for 20 min, washed with deionized water, and lyophilized.

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III. Results

Physicochemical Characterization: UGNPs had an average size of 126 nm, whereas UE-NPs and UAGG-NPs ranged between 100-200 nm and 200 nm, respectively. Zeta potential measurements indicated good colloidal stability, with UGNPs at +27 mV, UE-NPs at +30 mV, and UAGG-NPs at -25 mV. Morphological analysis confirmed spherical nanoparticles with well-defined structures in all formulations.

Encapsulation and Drug Loading Efficiency: UE-NPs exhibited the highest encapsulation efficiency (75%) and drug loading capacity (3.5 mg). UGNPs encapsulated 2.82 mg of UA within 100 mg of nanoparticles, achieving 69.98% efficiency. UAGG-NPs showed an encapsulation efficiency of 75%, indicating effective drug retention across all polymer systems.

In-Vitro Drug Release Profile: UE-NPs exhibited the most sustained release over 24 hours, likely due to Eudragit's polymeric structure. UGNPs showed controlled release, influenced by UA's hydrophobic nature and the compact Gum Acacia matrix. UAGG-NPs demonstrated a stable release profile suitable for prolonged bioactivity.

Antioxidant and Enzymatic Activity: UE-NPs exhibited the highest DPPH scavenging activity, outperforming free UA. UGNPs displayed a delayed but effective antioxidant response, suggesting gradual radical scavenging. AChE inhibition analysis revealed that UGNPs exhibited inhibition levels comparable to Rivastigmine, supporting their potential in neurodegenerative disease therapy.

The bar charts visualizing the comparative physicochemical characterization of the three UA-loaded nanoparticle formulations, including particle size, zeta potential, encapsulation efficiency and drug loading are illustrated in figure 4. With their exceptional drug loading sustained release and encapsulation efficiency UE-NPs are perfect for long-term drug delivery. UGNPs demonstrated their neuroprotective potential by offering good stability and controlled release with AChE inhibition levels that were on par with rivastigmine. Because of their good drug retention and steady release profile UAGG-NPs may be advantageous for long-term bioactivity.

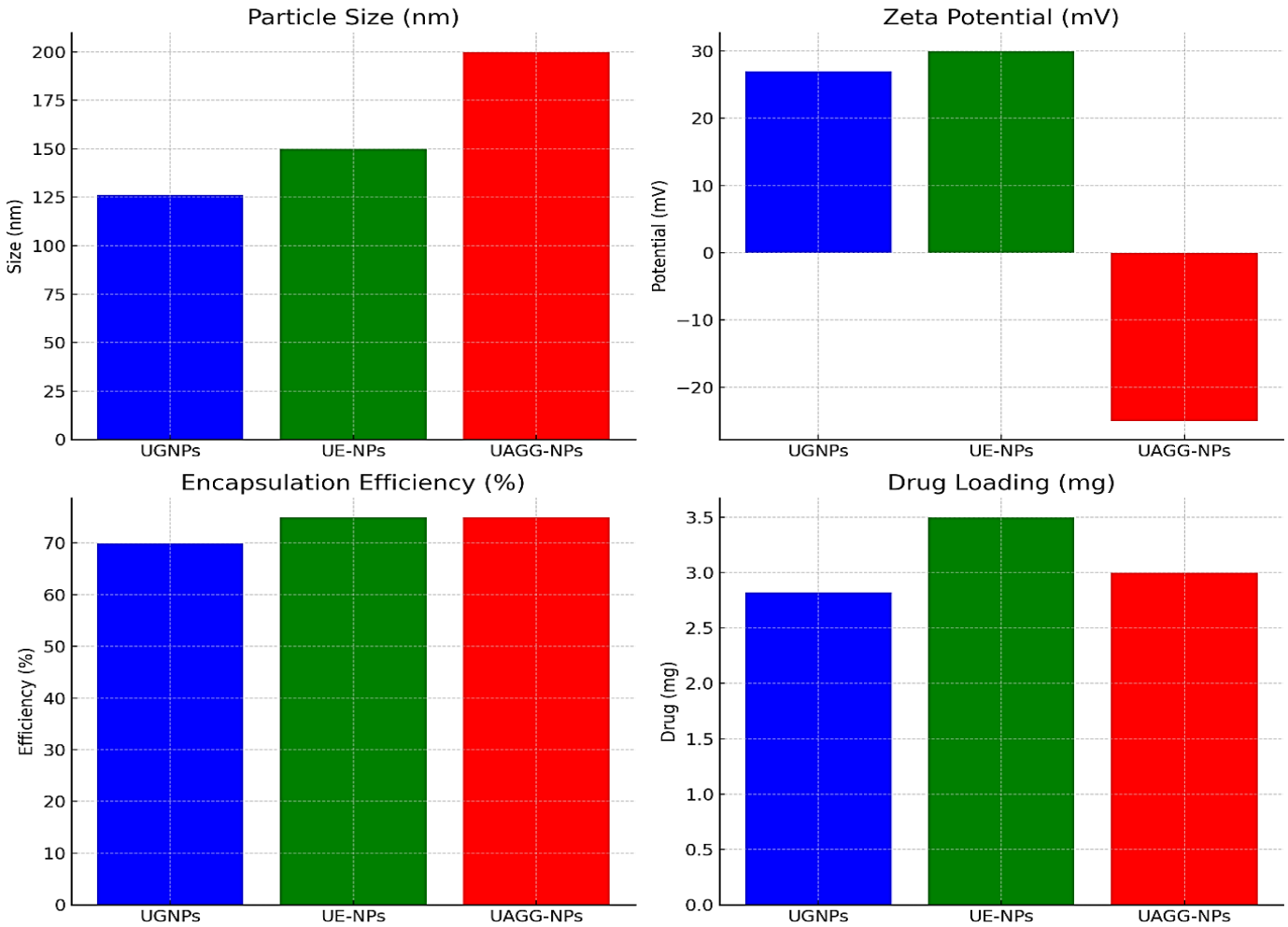

Figure 4. The comparative physicochemical characterization of the three UA-loaded nanoparticle formulations, including particle size, zeta potential, encapsulation efficiency and drug loading are depicted here.

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IV. Discussion

In the context of Alzheimer's disease (AD), ursolic acid's (UA) neuroprotective qualities have attracted a lot of attention. Because of its numerous mechanisms which include acetylcholinesterase (AChE) inhibition, oxidative stress reduction and neuroinflammation suppression, UA is a promising therapeutic candidate. Nevertheless, its low bioavailability and poor aqueous solubility have impeded its clinical use. Potential answers to these problems are provided by recent developments in drug delivery systems based on nanotechnology which improve the pharmacokinetic and pharmacodynamic profiles of UA [5].

Inhibiting AChE, an enzyme that breaks down acetylcholine is one of UA's main neuroprotective abilities. Cholinergic signaling which is essential to AD pathology is improved by this inhibition. According to studies, UA has a strong AChE inhibitory effect that is on par with that of common AChE inhibitors used to treat AD like tacrine and donepezil. Research has demonstrated for example that UA from Origanum majorana L. has the potential to be a therapeutic agent for AD because it's dose-dependently inhibits AChE activity with an IC_{50} value of 7. 5 nM [2].

Notwithstanding these encouraging pharmacological effects, UAs low bioavailability and poor aqueous solubility restrict its clinical use. It is difficult for traditional formulations to achieve sustained drug release and efficient blood-brain barrier penetration. Nanotechnology-based drug delivery systems improve UAs pharmacokinetic and pharmacodynamic characteristics providing workable answers. The potential of various nanoformulations to enhance drug solubility, stability and targeted delivery has been thoroughly investigated. These include metal nanoparticles, polymeric nanoparticles and lipid-based nanoparticles. Polymeric nanoparticles have demonstrated promise in augmenting the neuroprotective efficacy and bioavailability of UA. The longer circulation time and increased cellular uptake of these nanoparticle formulations result in improved therapeutic effects and sustained drug release [6].

Amyloid β buildup, oxidative stress, neuroinflammation and synaptic dysfunction are the hallmarks of Alzheimer's disease which result in neurodegeneration and cognitive impairment. Because of its anti-inflammatory, antioxidant and anti-amyloid β qualities UA has become a viable option for addressing several pathological features of AD. UA-loaded nanoparticles may improve neuronal survival, decrease amyloid aggregation and restore synaptic function in addition to effectively crossing the blood-brain barrier according to recent research. Additionally, the potential of UA to improve mood disorders and cognitive function linked to neurodegeneration is highlighted by its capacity to modulate the monoaminergic system and regulate the expression of important proteins including choline acetyltransferase and vascular endothelial growth factor [1].

The potential of nanoparticle-based UA formulations in resolving the issues of poor solubility bioavailability and blood-brain barrier (BBB) penetration of ursolic acid (UA) for the treatment of Alzheimer’s disease (AD)and other neurodegenerative disorders is highlighted in this study. Polymeric nanoparticles lipid-based nanoparticles and metal nanoparticles are examples of nanotechnology-driven drug delivery systems that have been shown to enhance UA stability sustained release and targeted neuronal delivery. These improvements are essential for improving the pharmacokinetic and pharmacodynamic characteristics of UA which in turn help to improve neuroprotection, lower oxidative stress and lower amyloid β (Aβ) aggregation. Although, preclinical and in-vitro results point to encouraging results, in-depth in-vivo research is required to confirm the safety, efficacy and therapeutic mechanisms of UA-loaded nanoparticles. In particular pharmacokinetics, biodistribution, metabolic stability and long-term neuroprotective effects should be assessed in future studies concentrating on animal models of AD. Additionally; in order to determine an appropriate therapeutic window for clinical applications, dose optimization and toxicity assessments are necessary. One promising strategy for enhancing drug delivery bioavailability and therapeutic efficacy in AD is the use of UA-loaded nanoparticle formulations. To successfully translate into clinical practice however more thorough research is required including preclinical validation clinical trials and advanced targeting approaches.

V. Conclusion

This comparative analysis highlights the potential of nanoparticle-based delivery systems in overcoming the solubility and bioavailability limitations of Ursolic acid (UA). Among the three formulations studied, Eudragit-based nanoparticles (UE-NPs) demonstrated the highest encapsulation efficiency, sustained drug release, and enhanced antioxidant activity, making them the most promising candidate for therapeutic applications. However, Gum Acacia (UGNPs) and Gum Ghatti (UAGG-NPs) also exhibited significant advantages. UGNPs showed strong acetylcholinesterase (AChE) inhibition, suggesting potential for neuroprotective effects in Alzheimer’s disease and other neurodegenerative disorders, while UAGG-NPs demonstrated good biocompatibility and stability, making them suitable for antioxidant and anti-inflammatory therapies. Despite these promising findings, further research is necessary to establish the clinical relevance of these formulations. Future directions should include in-vivo animal studies to evaluate pharmacokinetics, biodistribution, and therapeutic efficacy in biological systems. Investigating these formulations for targeted drug delivery across the blood-brain barrier could open new avenues for neurodegenerative disease treatment, further reinforcing the importance of nanotechnology-based drug delivery in modern medicine.

List of Abbreviations

AD: Alzheimer's Disease

Aβ: Amyloid beta

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ROS: Reactive Oxygen Species

UA: Ursolic Acid

BDNF: Brain-Derived Neurotrophic Factor

AChE: Acetylcholinesterase

NPs or nps: Nanoparticles

NFTs: Neurofibrillary Tangles

PD: Parkinson's Disease

FAD: Familial Alzheimer's Disease

BBB: Blood-Brain Barrier

CNS: Central Nervous System

FDA: The Food and Drug Administration

1H-NMR: Proton Nuclear Magnetic Resonance Spectroscopy

PSA: Particle Size Analyser

FTIR: Fourier Transform Infrared Spectroscopy

SEM: Scanning Electron Microscopy

TEM: Transmission Electron Microscopy

DSC: Differential Scanning Calorimetry

UGNPs: Gum Acacia Nanoparticles

UE-NPs: Eudragit Nanoparticles

UAGG-NPs: Gum Ghatti Nanoparticles

Additional Information

VI. Disclosures

Human subjects: All authors have confirmed that this study did not involve human participants or tissue.

Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue.

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following:

Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work.

Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work.

Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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