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Prospective Role of Citicoline and Hyaluronated Nanotechnology as Drug Delivery Approaches for Alzheimer's Disease: Review of the Literature

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Abstract

Alzheimer's disease (AD) represents a degenerative nerve disease that highly occurs in older people, which grow fast across developing countries. A precarious target in the controlling of AD aims at boosting presently accessible pharmacologic therapies' impacts, e.g., Cytidine diphosphocholine (CDP Choline or Citicoline). Citicoline (CT) denotes a food complement utilized as a manager with neuroprotection characteristics for neurological disarrays (including stroke, brain injury, AD, and dementia). Citicoline is a source of choline, which helps to maintain the consistency of neuronal cell membranes and is a significant intermediary in the creation of phosphatidylcholine (essential brain phospholipids). Companies chiefly market most approved drugs for controlling AD as traditional medicines taken via the mouth. Because of the gastrointestinal drawbacks and failure to target the brain, such medications, and dosage regimens obstruct patient obedience and cause stoppage of the treatments.

Nanotechnology-based drug delivery systems controlled in various ways are favorable tools in enhancing the compliance of patients and succeeding in improved treatment results. A viable, non-invasive way of delivering medicinal drugs to the brain while bypassing the blood-brain barrier (BBB) is intranasal administration. The literature article was searched in the National Center for Biotechnology Information Advances Science and Health (NCBI), Wiley online library, and Science Direct database utilizing the keywords Alzheimer's disease, Citicoline, and nanotechnology. Articles that appeared appropriate based on title and abstract were included. Also, an individual collection of literature reviews on the therapeutic effects of CT and the lipid-based vesicular system was referred. This article review discusses AD, pathogenesis, therapeutic objectives and treatments, CT therapeutics effect in AD and other central disorders, the types of nanocarriers, intranasal administration. and advantages in brain targeting.

Keywords

Alzheimer's disease; Theories of pathogenesis, Citicoline; The therapeutic effect of CIT in AD, Nano sizing lipid-based vesicles

1. Introduction

Alzheimer's disease (AD) poses substantial challenges to elderly patients, care providers, and healthcare systems owing to its increasing occurrence and socioeconomic problems among people who suffer from AD worldwide. The numbers of AD older people account for approximately 50–60% of all dementia [1, 2]. Alzheimer's disease represents the supreme normal prototype of dementia in the aging population [2]. Alzheimer's disease manifests as a result of neurodevelopmental problems brought on by an imbalance between the excitatory and inhibitory signals of the cerebral cortex and hippocampus [3]. According to recent research, neurofibrillary tangles of hyper phosphorylated tau proteins and extracellular precipitation of amyloid-beta (Aβ1-42) are two of the disease's main pathological characteristics [4]. These features are linked to the stimulation of the enzyme acetylcholine esterase (AChE), which results in the formation of insoluble Aβ plaques and causes neural cell death [5, 6]. Memory loss and cognitive dysfunction are consequently caused by these pathological changes to the brain structure in AD patients [7]. However, the extracellular matrix (ECM) is a significant essential regulator for the development of synapses and regulation of their function in the cerebral cortex [8] .

When the matrix organization is damaged or altered, it implicitly affects amyloid beta-42-a aggregation, synaptic plasticity, and neuronal function in AD [9]. Hyaluronic acid (HA), a crucial component in the brain and extracellular matrix, acts as a scaffold in the central nervous system (CNS) [10]. Through interactions with Hyaluronan neuronal cell surface receptors such Cluster of Differentiation 44 (CD44), Hyaluronan-mediated motility (RHAMM), and Intercellular adhesion molecule 1 (ICAM), it also regulates intercellular signaling [11].

Meanwhile, the central cholinergic system served as the primary centre of cognition [12]. Especially in the basal forebrain, frontal lobe, hippocampus, and brainstem, acetylcholine (ACh) is the predominant cholinergic neurotransmitter synthesized in the central neurons in responsibility for maintaining consciousness, recognition, thinking, and learning [13, 14]. Acetylcholine levels in the brain are noticeably lower in (AD), and indications of neurodegenerative dysfunction arise [15, 16]. Thus, the cholinergic strategy of utilizing acetylcholinesterase inhibitors (Ach EIs) has been considered a typical AD treatment and revealed indicative usefulness [17]. Acetylcholinesterase

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inhibitors such as galantamine (GAL), rivastigmine (RSM), and donepezil (DPZ) improve availability at the synaptic cleft by inhibiting the enzymatic breakdown of acetylcholine. Moreover, they can decrease disease progression through probably declining (Aβ) production and toxicity and promoting the expression of nicotinic receptors [18]. Although initial controlled clinical experiments revealed lower clinical utility in treating AD when using cholinergic precursors (such as choline and phosphatidylcholine), other ancestors demonstrated moderate benefit in cognitive decline [16]. As an illustration, the study of (IDEALE) reported elongated administration of Cytidine diphosphocholine (CDP Choline), also named Citicoline (CT) over about 3–6 months, evidenced safe and efficacious between older people having minor vascular cognitive deficiency [19, 20].

Citicoline was revealed an agent with neuroprotection characteristics in ischemia and hypoxia. It showed effectiveness in enhancing cognition [15, 20]. Citicoline accomplishes this by functioning as an endogenous source of choline, inhibiting apoptosis, enhancing neuroplasticity, activating phospholipid and acetylcholine manufacturing in the membrane of nerve cells, and increasing Sirtuin1 expression, among other pharmacologic actions [20, 21]. It has confirmed an exceptional safety profile with limited side actions to infrequent excitability, restiveness, self-limiting headaches, and digestive intolerance. [22]

However, when CT is administered orally or intravenously, it swiftly breaks down into cytidine and choline within a short period[23]. These two distinct metabolites are consumed by numerous organs in the body and then proceed to the brain. Even though the medicine has a bioavailability of over 90%, which indicates a very high rate of absorption, only 0.5% and 2% of the drug, when administered by mouth or intravenously, respectively, is actually delivered to the brain [24]. The hydrophilic nature of CT and its rapid metabolism, which is followed by liver uptake of the majority of the free choline, may help to explain this. This is the primary barrier preventing intact drug molecules from crossing the BBB [25] .

To achieve CT's therapeutic effect on AD, appropriate delivery nanocarriers must be created. Nowadays, nanotechnology is getting a lot of interest for the delivery of therapeutic drugs. It is a technology that enables the control, handling, research, and production of objects and structures with a "nanometer" size. These nanoscale structures, like nanoparticles, perform novel functions that are noticeably different from those of objects made of identical constituents [28] .

One of the most extensively researched groups of drug delivery technologies is nanoparticles (NPs) [26]. They have various distinctive properties and capabilities that can be utilized to improve traditional drug administration. Therefore, a lot of effort has been put into modifying modern nontherapeutic delivery systems for better treatment safety, patient compliance, and efficacy [27]. One of the major advancements made in this area of research recently is the targeting of drugs to specific organs using NPs [28]. The same specific organ encompasses both healthy and diseased parts, and illnesses exhibit a high degree of spatial variability within that specific organ [29]. Therefore, some drug delivery formulae would be capable of directly targeting the specific area affected by the disease.[30]

Considering that nanocarriers are able to overcome the rapid mucociliary clearance and subpar nasal absorption, the hypothesis of brain medication targeting employing nasal dosage form in the treatment of neurodegenerative illnesses has greatly benefited from nanoscience [31]. Nanocarriers distribution through the nose has several benefits, including successful brain targeting, ease of self-administration, and non-intrusiveness. Additionally, it becomes crucial to potentiate and attenuate a prospective payload by nanocarriers surface engineering. In order to facilitate specific uptake and persuading therapeutic efficacy[32 ,11] .

The preceding literature was determined to be devoid of sufficient information regarding any targeting CT delivery to the brain. Thus, the main goal of this review is to discuss and encourage the development of an effective nasal CT dosage form for the treatment of Alzheimer's disease and others neurological diseases.

2. Alzheimer's disease: Pathogenesis, Therapeutic Objectives, and Treatment Methods

Alzheimer's disease regression is slow and gradual, sometimes beginning 20 or more years prior to the appearance of medical symptoms [33, 34]. When it happens in a family, it is termed 'familial AD', accounting for almost 5–10% of AD patients [35]. In contrast, non-familial AD accounts for approximately 70% of AD patients caused by a mixture of genetic, lifestyle, and environmental reasons [35]. Authors suggested many explaining proposals of AD pathogenesis molecularly. Comprehending the essential factors in the pathogenesis of a nervous disease of AD helps determine potential therapeutic targets. Thus, AD is controllable by utilizing targeted or symptomatic disease adjusting treatments. The approaches of symptomatic treatments enhance memory and cognition, leading to an improved quality of life [36]. The suggested hypothesis of AD pathogenesis contains dissimilar methods according to Cholinergic, Excitotoxicity, Amyloid, and Tau theories (Fig. 1). Further to such main hypotheses, evidence shows that reactive oxygen species (ROS), inflammatory mediators, and nitric oxide could help in the neuropathogenesis of AD [37].

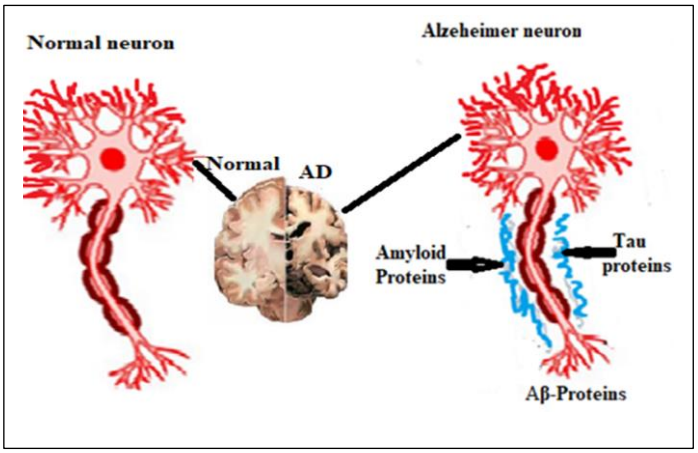

Figure 1. Normal and Alzheimer's neuron

2.1. Cholinergic theory

This theory represents the initial hypothesis that explains AD neuropathy genesis. Detecting decreased choline exploit and releasing acetylcholine for AD cases' brains showed considerable presynaptic cholinergic debit, causing memory diminishing, as well as cognition failure [37]. Cholinergic drugs represent cholinesterase inhibitors (ChEIs), which improve cholinergic neurotransmission as they prevent acetylcholine esterase (Fig. 2A). Galantamine, rivastigmine, and donepezil are three FDA-approved ChEIs[38] .

2.2. Excitotoxicity theory

The most critical receptor is N-Methyl-D-aspartate (NMDA), representing a memory function controller and synaptic plasticity [39]. In the case of binding glycine and glutamate to NMDA, stimulation takes place, permitting Ca2+ and Na+ influx (Fig. 2B) .

It was informed that NMDA receptors' hyper excitability encourages Ca2+ overload, activating several consequent actions, causing apoptosis by the end [39]. The FDA-approved memantine (Glutamatergic medicine) denotes uncompetitive NMDA receptor antagonists for the symptomatic therapy of modest for serving AD [40] (Fig. 2B).

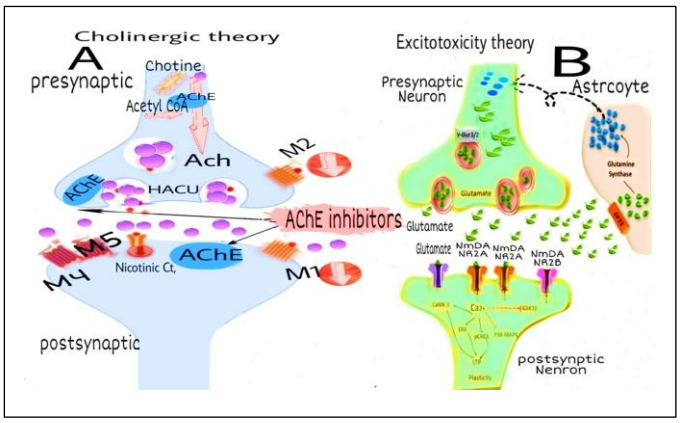

Figure 2. Schematic diagram showing Cholinergic and Excitotoxicity theory in AD

2.3. Amyloid theory

Amyloid ancestor protein (APP), which is known as a type1 of transmembrane protein (glycoprotein), is represented by various human cell kinds. APP proteolysis process is arranged by α-, β- and γ-secretases (Fig. 3). The amyloid hypothesis suggests that altered APP proteolysis pushes perceiving amyloid proteins Aβ-42 which successively cumulative into plaques, fibrils, and oligomers. Such toxic collected protein aggregates induce cytotoxicity and neurodegeneration, unavoidably causing dementia appearances (Fig. 3) [41, 42]. Glenner and Wong (1984) efficaciously recognized and purified amyloid protein Aβ in the cerebrospinal fluid of AD cases [43]. Hence, a lot of anti-amyloid therapies were projected and explored, such as semagacestat and rosiglitazone[17] .

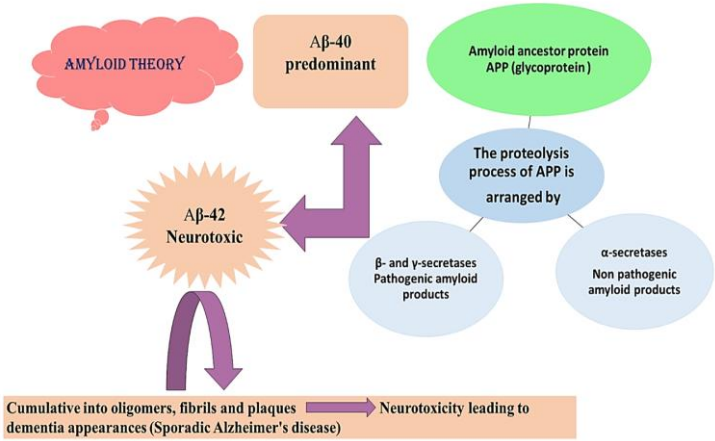

Figure 3. Schematic diagram of Amyloid Theory

2.4. Tau theory

The normally developed neuron contains three microtubule-bonded protein (MAP) taus, namely MAP1A, MAP1B, and MAP2, that stimulate microtubules' stability and assembly [40, 44]. The phosphorylation degree controls the biological action of tau [45]. In AD patients' brains, tau undergoes irregular hyperphosphorylation that damages its binding to microtubules and causes perceiving neurofibrillary tangles and dementia[45]. Numerous anti-tau drugs were studied, comprising nicotinamide and valproate [17, 40] (Fig. 4).

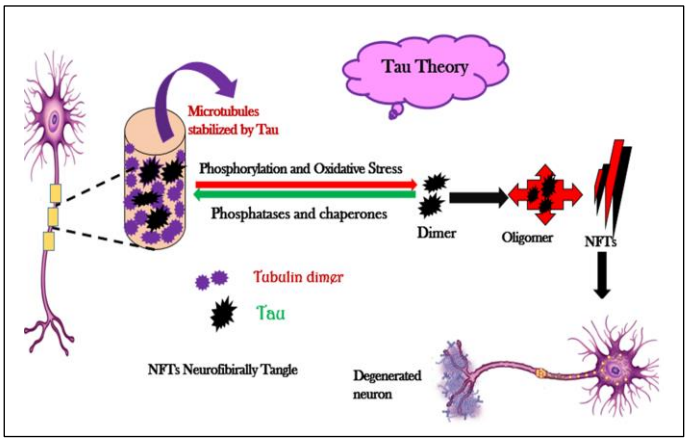

Figure 4. Schematic diagram of Tau Theory

3. Citicoline (CDP-choline)

Citicoline denotes an intermediate organic compound (Fig. 5) in the biosynthesis of phospholipids of the human cell membrane [46]. This compound was exposed to neuroprotective therapeutic influences in several models of central nervous system damage [47]. Further, CT demonstrates a positive neurotherapeutic influence in the contexts of hypoxia, ischemia, and enhanced learning and memory function in animal brain aging models [46]. CT is a part of the cluster of biomolecules in living organizations termed "nucleotides", showing significant functions in cell metabolism [48] .

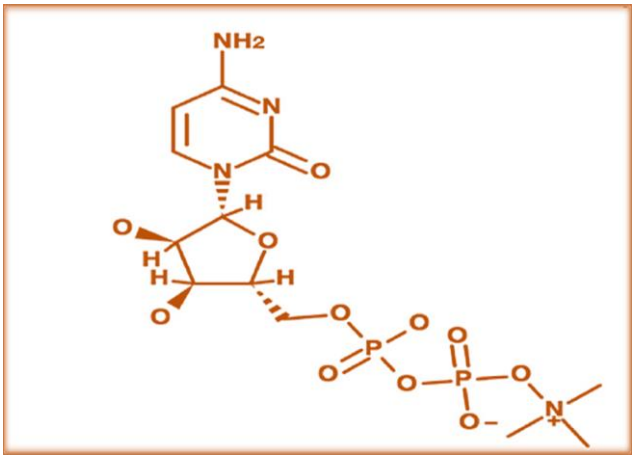

Figure 5. Chemical structure of Citicoline

The primary structure of a nucleotide includes ribose with cytosine and a phosphate group. CT contains ribose, pyrophosphate, a nitrogenous base (cytosine), and choline [46]. Combined with B vitamins, choline represents a trim ethylated nitrogenous base, passing in three main pathways of

metabolism: The first one is phospholipid synthesis by phosphorylcholine; the second is acetylcholine synthesis, and the third is oxidation to betaine that assists as a methyl giver [48]. The construction of endogenously CT considers the rate-limiting stage in synthesizing phosphatidylcholine (the major membrane phospholipid) from choline [48]. Exogenous CT, which is the form analyzed in the intestine and freely consumed as a form of choline and cytidine, penetrates numerous biosynthetic pathways, which operate CT as an intermediate. Therefore, CT makes a cautious impact on systemic choline assets and prevents the analysis of cell membrane phospholipids [49]. Finally, it is useful in several neurological disorders, probably due to its capability to improve the function and integrity of the membrane of nerve cells. CT results from the enzymatic process of orotic acid and choline chloride. CT is marketed as a food complement in the USA and medicine in Japan. Its sodium salt utilized for clinical trials is a white powder sold as a drug across Europe [48].

3.1. Pharmacokinetics and Metabolism of Citicoline

Citicoline represents a water-soluble complex having over 90% bioavailability [50]. Pharmacokinetic research on adults (healthy people) illustrates that oral doses of CT are absorbed fast, but below 1% is released in feces. Plasma levels peak of CT biphasically, at first one hour following ingestion just before a second higher peak at 24 hours after the dose. Exogenous CT form is metabolized in the liver and gut wall. The results form of exogenous CT made by hydrolysis process in the intestinal wall is cytidine and choline that are circulated in the body after absorption, arriving at a systemic circulation to be used in several biosynthetic pathways. Finally, they cross the barrier between the brain and blood to be recombined into CT in the brain[51]. Pharmacokinetics illustrate that CT elimination happens chiefly by respiratory CO2 and urinary excretion in two stages, reflecting the peaks of biphasic plasma. Following the primary peak of the plasma concentration, it declines sharply and slows over the following 4-10 hours. During the 2nd stage, the elimination rate declines more slowly following the fast decline after the 24-hour plasma peak .

The elimination half-life takes place from 56 to 71hours regarding CO2 and urinary excretion, respectively [52]. Cytidine (a key constituent of RNA) is undergoing cytoplasmic transformation to CTP [53]. In the CT pathway of metabolism, choline undergoes phosphorylation by the enzyme choline kinase; the resultant phosphorylcholine associates with CTP to create CT [54]. In this reaction, the associations of CT and diacylglycerol (DAG) create phosphatidylcholine via the choline phosphotransferase catalyst enzyme [50]. The oral method of CT elevates cytidine and choline plasma levels in rats from 6 to 8 hours. Elongated administration takes 42 and 90 days and increases the cerebral concentrations of the three main phospholipids in the brain cells membrane (phosphatidylserine, phosphatidylethanolamine, and phosphatidylcholine). A study discussed confirming the vital part of such metabolites for phosphatidylcholine biosynthesis by providing rats with daily doses of CT via the mouth for three months. At the daily dose of 500 mg/kg, the levels of phosphatidylethanolamine improved by 17%, phosphatidylcholine by 25%, and phosphatidylserine by 42% [55].

The administration of CT to elderly rats stimulates CTP: phosphatidylcholine transferase, which is the rate-limiting catalyst enzyme in the CT pathway of phosphatidylcholine synthesis [56]. In absorption, the main released metabolites through analyzing CT are cytidine and choline. In younger and older cases, a single CT oral dose elevates plasma choline levels. Utilizing the protein magnetic resonance spectroscopy (PMRS) illustrates diminishing brain choline levels in elder cases after CT administration and improvement in young cases. This finding explains that CT cytidine moiety might be elevated by brain cells in elder cases more speedily than choline. Thus, a recommendation is made that cytidine is the CT constituent firstly in charge of activating phosphatidylcholine synthesis in elder cases [57]. Utilizing the (PMRS) illustrates that CT administration to elder cases for six weeks raises brain levels of phosphodiesters known as phospholipid metabolism byproducts. Confirmation that CT enhances phospholipid synthesis and turnover that can assist inverse aging-related cognitive dysfunction[46] .

3.2. Role of Citicoline in Alzheimer's disease

According to the key function of CT as an intermediate of phosphatidylcholine biosynthesis, authors theorized that CT would switch histopathological alterations that depend on the age inside the neuronal membrane of the brain, thus maintaining memory function[15] .

Citicoline as a prospective medication for aging-related amnesia was discussed in five trials [58-61] in cases with AD. In 1994, Camargo et al. accompanied a double-blind study to define how a one-month administration with CT affects cognition in twenty AD cases [58]. Following CT oral administration (1,000 mg/daily), cognitive function evaluated by the Mini-mental test examination (MMSE) marginally developed in an EOAD case subgroup, as exposed by a minor, though highly significant ($p<0.005$) rises in MMSE marks. MMSE marks are reduced in cases in later AD stages. The total group showed enhanced spatial-temporal orientation, with a better noticeable change in AD cases. In 1999, Alvarez et al. conducted a double-blind, placebo-controlled group to test the therapeutic effects of CT on 30 cases (from mild to moderate) with senile dementia of the AD type [59]. The CIT dose is 1,000 mg daily and was administered over 12 weeks. The overall results revealed an insignificant change trend among the CT and placebo groups in favor of the actively treated group. Citicoline revealed slightly elevated cerebral blood flow and rates than the placebo group. The mechanisms of action depend on CT's noticeable function as a cholinergic system activator through acetylcholine biosynthesis and stimulation of muscarinic receptors in the central nervous system. According to clinical data, CT confirmed a potential ability to enhance AD-related cognitive performance.

3.3 .Other Therapeutics Effects of Citicoline

3.3.1. Stroke Therapy

Citicoline was assessed in stroke cases in controlled experiments. A double-blind, placebo-controlled experiment measured the therapeutic impact of CT on 272 stroke cases in the acute stage (from moderate to severe) cerebral infarction with mild to moderate disorders in consciousness [62]. For fourteen days, the authors gave 133 cases in the CT treatment group 1,000 mg/ day CT through intravenous administration. Unlike the other 139 cases in the placebo group, the CT groups showed enhanced levels of consciousness significantly. At the completion of the trial period, 54% of cases on CT improved in comparison to 29% of placebo cases. The findings propose that intravenous CT stimulates recovery from reversible tissue impairment in the acute phases of the stroke while reducing aggravated post-stroke symptoms. Other experiments administered CT to post-stroke cases, showing comparable

findings with the above study, such as enhanced recovery with improved parameters of neurological function, including muscle strength, ambulation, and cognition. A recent analysis of these studies shows that using CT in the first 24 hours after stroke onset increases the potential complete recovery during three months[63] .

3.3.2. Brain Injury

Brain injury outcomes from reducing human cell membrane phospholipids, before intracellular cerebral edema because the sodium-potassium pump breaks down [48]. In a single-blind randomized experiment, 216 cases with injuries were allocated to two treatment groups. While the first group, i.e., control, was offered traditional treatment, the other was offered traditional treatment along with intravenous CT with a dose of 1,000 mg per day. The section of cases displaying improved cognitive and motor symptoms was superior in the CT group; the death rates were the same in both groups [64].

3.3.3. Glaucoma

Outcomes of two open experiments propose that treatment with CT improves the impairment of the optic nerve in glaucoma [65]. CT takes place to support neuroprotection of the retina by improving the synthesis of phosphatidylcholine. Glaucoma, a principal reason for blindness in older people, represents a neurodegenerative disease categorized by apoptosis of retinal ganglion cells. Impairment of the retina can happen prior to noticeable blindness [66]. A double-blind (placebo-controlled experiment) as a short-term administrated dose of 1,000 mg CT by daily intramuscular injection enhanced visual and retinal function in people with open-angle glaucoma [67]. The trial proposed that dopaminergic activation is a key mechanism for CT's impact on the retina [63]. Verifying this hypothesis was supported by a current animal trial screening that CT increases the retinal dopamine concentration in rabbits [68]. CT (1,000 mg/ day) used through intramuscular injection considerably developed visual acuteness in amblyopia cases [70 ,69].

3.3.4. Parkinson's Disease

According to CT's hypothetical capability to enhance dopaminergic function, a double-blind crossover experiment was assessed on cases with Parkinson's disease who underwent treatment with L-dopa in addition to a decarboxylase inhibitor. Enhancements in bradykinesia and inflexibility in cases administered CT (500 mg/ day through intramuscular injection) in comparison to placebo patients; the tremor was unaffected [71].

3.3.5. Vascular Dementia

A minor, double-blind clinical experiment revealed the lack of impact of CT therapy in 30 cases aged 55 or more (moderate to severe) with vascular dementia (VaD). It omitted cases with a head injury, AD, brain stroke, or any other severe neurological illnesses. VaD diagnosis was constructed on brain abnormalities evaluated by MRI in addition to a battery of neuropsychological tests, evaluating the cognitive and psychomotor functions. It administrated fifteen cases of a 500 mg CT tablet twice a day. In contrast, 15 cases were provided with placebo tablets. Results were evaluated after half a year and a year. The study reported the lack of changes in the placebo groups and treatment in neuropsychological function at the start and end of the trial. MRIs exhibited brain pathology exacerbation in the two groups resembling the former trial [72]. Fig. 6 summarizes the therapeutics effect of CT.

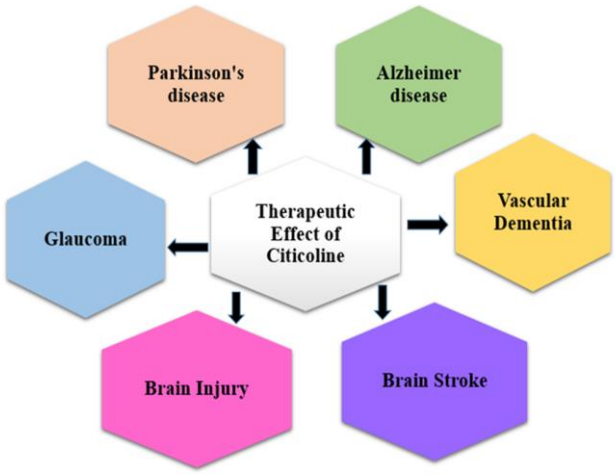

Figure 6. The therapeutics effect of CT.

4. Nanotechnology as drug delivery approaches in AD

According to the data described above, the therapeutic objectives targeting controlling AD development or symptoms should behave centrally in the brain. Currently, the approved FDA medications are marketed as oral formulae (excluding rivastigmine presented as a transdermal patch). The oral formulae of centrally acting drugs require utilizing the highest doses, making the little portion crosses the brain after resolving all oral barriers of (distribution, liver metabolism, and absorption), and lastly, crossing the blood-brain barrier (BBB) is significant therapeutically. Moreover, a lot of such dosage forms demonstrate a massive occurrence of side effects because of their actions in the peripheral tissues (e.g., diarrhea, vomiting, and nausea) [73]. Reducing such side effects enhances the case's quality of life. Additionally, administered free medicine has to combine with serum albumin to show effectiveness in half-lives in the blood circulation. However, nanocarriers are not dependent on albumin binding for their half-lives[74] .
Furthermore, they are administrable intranasal, totally sidestepping the BBB that exploits the therapeutic results and diminishes the side effects [75]. Current nanotechnological developments offered outstanding chances for controlling CNS diseases. Encapsulated a drug in an appropriately formed nanocarrier may raise drug concentrations in the brain cells contrasting the drug alone if this nano formula is capable of passing the BBB and collecting in the right neuronal cell[76]. Additionally, nanocarriers may modify targeting moieties to bind especially supposed receptors or transporters apparent at the BBB, improving CNS permeability and selectivity [40].

Role of Hyaluronic acid

Hyaluronic acid (HA), a crucial component in the brain and extracellular matrix, acts as a scaffold in the central nervous system (CNS) [10]. It is a negatively charged nonsulfated glycosaminoglycan (GAGs) that is essential for inflammation under sterile conditions [77, 78]. In contrast to sulfated GAGs [79, 80], no A fibrils are seen in the presence of HA [81, 82]], according to recent research, which showed sulfated GAGs are linked to amyloid genesis[83-85], As a result, HA expression and dispersion would be a crucial regulator of AD development.

The number of repeats of the HA disaccharide determines the MW of the HA polymer, which ranges from 5 to 10,000 kDa. The small HA polymers perform angiogenic [86, 87], inflammatory [88]and immunostimulatory roles[89]and are regarded to be "danger signals" in the body[90]. In contrast, the high MW HA polymers occupy space and have regulatory and structural functions in the body. Three distinct isoenzymes (Has1, Has2, and Has3) manufacture HA in mammals [90, 91] . Biochemical characteristics of distinct isoenzymes (HASs) vary[92]. Has1 and Has2 synthesize HA polymers with high MW chains (more than2 × 10), but Has3 is the most active HAS and creates HA polymers having shorter chains (less than2×105 Da) [93].

It's necessary to understand how HA-mediated signaling regulates synaptic function in addition to HA production. Despite the fact that HA is a molecule that fills empty spaces, it also influences intercellular signaling by interacting with hyaluronan neuronal cell surface receptors like CD44, RHAMM, and ICAM [11]. The nervous system's ECM is remodelled as a result of the breakdown of hyaluronic acid brought on by an overactive inflammatory reaction carried on by tissue damage and neurological disease [94]. The microRNA-137(miRNA), which blocks pro-inflammatory responses by targeting ICAM-1 and CD44, and tumor necrosis factor-alpha induced protein 1 (TNFAIP1), which prevents AD-related neurological diseases, can both regulate the NF-kB pathway. Additionally, when miRNA-137 is overexpressed in neurons, the NF-kB pathway is blocked [95]. This review was conducted to explore the potential role of implementing (HA), a key component of the ECM, as the natural legend and a surface-bound targeting moiety for neural cell surface receptors in brain cells .

Drug delivery systems that are derived from lipids take four categories: Emulsion-based systems, solid lipid particulate dosage forms solid lipid tablets, and vesicular systems.

4.1 .Emulsion Based Systems

4.1.1 .Dry emulsions

Dry emulsions are lipid-based powder formulas that can be used to recreate an o/w emulsion in vivo or in vitro [96]. They are made by drying liquid o/w emulsions with a solid carrier in the aqueous phase. Because of their stability and impact of prolonged release, dry emulsions are of interest. They offer a viable oral drug delivery strategy for medications that are light- or oxidation-sensitive, sparsely soluble in fat, and that are lipophilic[97]. Spray drying, lyophilization, and rotary evaporation are methods that can be used to create dry emulsions. Solid carriers made of water-soluble polymers, such as hydroxyl propyl methyl cellulose, methyl cellulose, and povidone, are utilized to prevent stability problems[96] .

4.1.2 .Microemulsions

Droplet sizes below 1 nm, often between 20 and 200 nm, are considered to be nanoemulsions [98]. Nanoemulsions are employed as carriers for hydrolyzable, lipophilic medicines because they are biodegradable, biocompatible, and simple to make. They are used as a sustained release delivery technique for subcutaneous injection depot formation [99]. They have a very high interfacial area and a good drug release profile [100]. Deliveries via parenteral, oral, ophthalmic, pulmonary, and cutaneous routes have all been explored and produced using nanoemulsions[101] .

4.1.3 .Self-emulsifying formulations

Self-emulsifying drug carriers are isotropic mixes of oil, surfactant, co-surfactant, and the drug ingredient that emulsify under gentle agitation [102]. Self-emulsifying drug delivery systems have the following benefits: more reliable drug absorption; selective targeting of drug(s) toward specific absorption window in gastrointestinal tract; protection of drug(s) from gut environment; control of delivery profiles; reduced variability, including food effects; enhanced oral bioavailability enabling reduction in dose; and high drug loading efficiency [103, 104]. Utilizing methods like melt granulation, self-emulsifying formulates have been converted into solid dosage forms. It is also possible to create powder form compositions using spraying techniques. These methods make it possible to create granules or powders that can later be compacted into tablets or put inside of capsules[105] .

4.1.4 .Pickering emulsions

Pickering emulsions, which are lipid-based emulsions with inner nanostructures maintained only by solid particles like silica, clays, calcium carbonate, titanium dioxide, latex, and many more, are a type of emulsion. The addition of solid particles will adhere to the interface's surface and stop the droplets from coalescing, making the emulsion more stable. Due to the increased adhesion potential of Pickering emulsions, the skin absorption of caffeine from silica supported Pickering emulsion was three times higher than that from surfactant maintained emulsion[106] .

4.2. Lipid Particulate Systems

Due to their special size-dependent characteristics and capacity to fit drugs into nanocarriers, lipids of biocompatible microparticles and nanoparticles have developed as promising polymer carriers. Physiologically compatible and physicochemically stable carrier systems, controlled drug release, increased levels of drug targeting, large-scale production at a relatively low production cost, protection of incorporated active compounds against degradation, and simple scale-up are some advantages of lipid particulate systems [107].

4.2.1. Lipid nanoparticles

Innovative carrier systems such as lipid drug conjugates, solid lipid nanoparticles, and nanostructured lipid carriers help to solve the issues mentioned above [108]. Physiological lipid is distributed in water or an aqueous surfactant solution to form solid lipid nanoparticles, which are sub-micron colloidal carriers. Due to the numerous drawbacks of polymeric nanoparticles, such as their cytotoxicity following internalization into cells and the difficulties of producing them on a large scale, lipids found naturally in the body or used as drug carriers are used instead.[109]. The use of physiological lipids, the avoidance of chemical solvents, and the possibility of a broad application range (topically, orally, and intravenously) are advantages of solid lipid nanoparticles [110]. Poor drug loading capacity, particle growth, unexpected gelation behaviors, drug expulsion following polymeric transition during storage, and greater water content of the colloidal (70–99.9%) have all been noted as potential drawbacks. [111]. The fluid lipid phase of nanostructured lipid carriers is said to be localized at the surface of solid platelets and the surfactant layer, or it has been claimed to be embedded within the solid lipid matrix. [112]. The problems of SLNs are reduced or completely avoided by nanostructured lipid carriers systems[113] .

4.3. Solid Lipid Tablets

Recently, solid lipid tablets have been made via moulding [114]. Lipids like phosphoglycerides and triglycerides are used in this approach. In the lipid matrix, the medication is dissolved or dispersed, and tablets are made by moulding with a tablet mould. The production of solid lipid tablets containing indomethacin and diclofenac potassium revealed sustained release qualities for once-daily treatment as well as ulcer inhibition potentials. Low cost of components, low cost of technologies, higher oral bioavailability, and fewer adverse effects are benefits of lipid-based tablets[115] .

4.4. Vesicular Drug Delivery System

Nanovesicles are colloidal particles in which a small, intracellular membrane encircled sac supplies or transports both hydrophobic and lipophilic drugs within a cell [116]. Nanovesicular systems offer attractive advantages, such as biodegradability, non-toxicity, amphiphilic nature, and the possibility of modifying drug bioavailability [117]. They require simple formulation procedures and can be established by optimizing their composition [118]. In general, lipid nanovesicles consisting of natural or synthetic phospholipids are named liposomes, whereas those composed of surfactants and cholesterol are named niosomes [117, 119]. Developed liposomal systems include transferosomes containing a surfactant as a vesicle edge activator and ethosomes consisting mainly of ethyl alcohol as a penetration enhancer [120, 121]. Furthermore, niosomes containing bile acids termed bilosomes exhibited improved stability in the attendance of bile acids in their structure [122]. Fig.7 summarizes some different modified lipid vesicle, which is effectively useful for targeting the AD brain, as shown below.

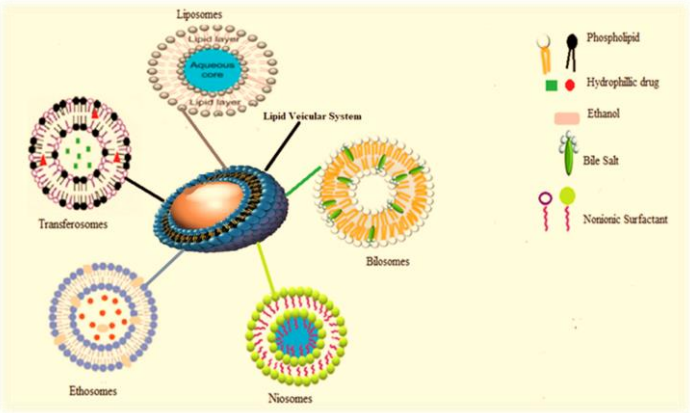

Figure 7. Schematic diagram of different types of lipid vesicles

4.4.1. Liposomes

Bangham and others discovered liposomes in the early 1960s and afterward developed the most widely discovered drug delivery system [123].

In terms of structure, liposomes are integrated bilayer vesicles containing a membranous lipid bilayer vesicle, which surrounds an aqueous volume that mostly consists of phospholipids. The greatest common natural phospholipids are soybean phosphatidylcholine (SPC) [124]. The preparation of liposomes takes various sizes with a range from50 nm to 100 μm. Rendering to the phospholipid's kind and the industrial method, they can contain diverse surface charges and uni-, bi, or multi-layer structures. Furthermore, the alterations of their compositions cause the development of various developed liposomes, e.g., transferosomes, ethosomes, and phytosomes [54–57]. As phospholipids, liposomes are non-toxic and biocompatible [54, 58]. Liposomes enclose drugs within a lipid bubble. Thus, they contain both hydrophilic and lipophilic drugs, causing the protection of drugs from enzymatic degradation and improving therapeutic efficacy [59]. Several studies were carried out on systems relying on liposomes as suitable carriers for improving AD treatment (Table 1) .

Studies explored the brain bioavailability of liposome-encapsulated drugs. Because of being very lipophilic, liposomes are expected to be optimal brain-targeting carrier systems [60, 61]. Nevertheless, authors find it hard to understand the exact mechanisms of BBB penetration. The endocytic passageway signifies imperative transportation for nanoliposomes with a diameter that may be equal to or less than 100 nm because their tiny size is similar to that of the brain endothelial cell. In contrast, larger liposomes (N100 nm) can easily pass through the brain's leaky capillaries [62]. Table 1 shows the comparative features of liposomes, transferosomes, ethosomes, niosomes, and bilosomes.

4.4.2. Some different forms of developed liposomes

4.4.2.1. Transferosomes

Transferosomes represent a distinctive kind of liposomes comprising phosphatidylcholine and a surface-active agent that acts as a lipid edge activator [125]. Authors introduced this kind to utilize phospholipids vesicles as transdermal nanocarriers. Such self-optimum collections, with the ultra-deformable vesicle membrane, are intelligent to transport the medicine replicable via the skin layer according to the best application choice with high proficiency [126]. Such lipid vesicular transferosomes represent numerous orders of magnitudes more deformable than the classical liposomes, making them suitable for the penetration of the skin. Transferosomes overawed the penetration of the skin trouble by pressing themselves along the intracellular closing lipid of the stratum corneum (SC). Transferosomes vesicles may move large molecules that are too huge to spread via the skin, e.g., the systemic delivery of therapeutically significant volumes of macromolecules, including interferon or insulin[128 ,127] .

4.4.2.2. Ethosomes

The minor modifications of liposomes are called ethosomes, representing a famous drug delivery system. Because they are soft, malleable lipid vesicles, researchers use them for improved delivery of therapeutic agents. Ethosomes are vesicular systems consisting primarily of propylene glycol, ethanol, phospholipid, and water [129]. Dissimilar classical liposomes that mostly deliver medicines to the outer layers of skin, ethosomes were exposed to augment permeation via the SC barrier [130]. They capture therapeutic agents with different physicochemical features, namely lipophilic, hydrophilic, or amphiphilic[131] .

4.4.2.3. Niosomes

They fundamentally represent non-ionic surfactant-based vesicles (uni or multilamellar) with an aqueous part surrounded by a membrane created from the association of surfactant molecules as lipid bilayers. Preparing niosomes can be achieved by many techniques, including ether injection, handshaking method, reverse stage evaporation, and extrusion aqueous dispersion [132] .

Table 1: Comparative features of liposomes, Transferosomes, Ethosomes, Niosomes and Bilosomes

Parameter	Liposomes	Transferosomes	Ethosomes	Niosomes	Bilosomes
Vesicular system	Bilayer lipid Vesicle	2nd generation lipid vesicle	3rd generation lipid vesicle	Non-ionic surfactant vesicle	Lipid vesicle-based bile salt
Structure	Natural phospholipid and cholesterol	Phospholipid and surfactant or edge activator	Phospholipid and ethanol or propylene glycol	Non-ionic surfactant and cholesterol	Phospholipid or non-ionic surfactant and bile salt
The flexibility of the lipid-based vesicle	Rigid in nature due to the presence of cholesterol in their structure	Ultra-flexible liposome and high deformability due to surfactant	Elastic liposome high elasticity and deformability due to ethanol	Slightly deformable	High deformability due to the presence of bile salt in their structure
Chemical stability of the vesicular system	Phospholipids undergo oxidative degradation	No particular trend determined	Stable than classical liposome	Moderately stable	Highly stable
Route of administration	Oral, parenteral, topical, intranasal, and transdermal	Topical, transdermal, buccal, and intranasal	Topical and transdermal	Oral, buccal, intranasal and topical, and transdermal	Oral, buccal parenteral, topical, intranasal and transdermal
GIT stability	Unstable	Nil	Nil	Unstable	Highly stable
Permeation mechanism	Diffusion, fusion, and lipolysis	Osmotic gradient existing across the different skin layers and Deformation Lipid Vesicle	Lipid perturbation, ethanol is used as a penetration enhancer which diminishes the glass transition temperature of lipids of vesicles and skin	Adsorption and fusion of the vesicle	Fluidizing and destabilizing the lipid bilayer of the vesicular system and the stratum corneum and providing further flexibility to the vesicular system. Bile salt, as a permeation enhancer, alterations the keratinized layer of skin, and the polarity in the subcutaneous lipid region enhances transcellular permeation
Gastric irritation	Low	Nil	Nil	High	Low
Drug leakage in GIT	High	Nil	Nil	High	Negligible
Storage and handling condition	Require a special storage condition as liquid nitrogen storage	No particular trend determined	No particular trend determined	Do not necessitate a unique storage condition	Do not necessitate a unique storage condition

4.4.2.4. Bilosomes

Bilosomes (BLS) are locked bilayer nanovesicles consisting of non-ionic surfactants and deoxycholic acid integrated into the liposome membrane [133]. In the pharmaceutical industry, bile salts are usually utilized as penetration enhancers to advance the bioavailability of drugs [134, 135]. BLS represent a new generation of nanocarriers due to their superior stability compared to classical liposomes. They were described by Mann et al. (2004) as an advanced non-ionic surfactant vesicle (NISV) with liposome-like structures and stabilized with bile salts for vaccines' oral delivery [136]. To circumvent the issues in GI transit, BLS were produced that hindered antigens from degradation and improved mucosal penetration [137]. BLS-based vaccine formed both systemic and a mucosal immune response that equaled the immune response developed through the subcutaneous route [138]. Rare studies have been published on BLs for intranasal drug delivery. [139]. However, their nanosize structure related to having bile salts and surfactants makes them promising candidates for intranasal application.

5. Intranasal Route

Intranasal administration offers a feasible, non-invasive way to get therapeutic agents via the BBB and into the brain [140, 141]. Drugs that cannot cross the BBB can now be given to the central nervous system in just a few minutes due to this approach. Additionally, it delivers medications to the brain directly after they have successfully crossed the BBB, eliminating the need for systemic delivery and any potential negative effects. This is made possible by the distinct connections between the brain and the outside environment that the olfactory and trigeminal nerves offer [140] .

The olfactory system and associated memory regions that are impaired by AD can be targeted with a wide range of treatments, including both small molecules and macromolecules [142]. Researchers have restored memory in a transgenic mouse model of Alzheimer's disease by using the intranasal delivery technique to stop neurodegeneration. In animal models, it has been demonstrated that the intranasal administration of insulin-like growth factor-deferoxamine, erythropoietin, and protects the brain from stroke [143, 144]. For the treatment of neurodegeneration, intranasal administration of the neuroprotective peptide NAP has been employed. Epidermal growth factor and intranasal fibroblast growth factor-2 have been found to promote neurogenesis in adult animals [145]. Even in healthy adult individuals with normal memory and mood, intranasal insulin improves memory, attention, and functioning in patients with Alzheimer's disease or moderate cognitive impairment [146]. The way Alzheimer's disease, stroke, and other brain illnesses are treated may be completely altered by this innovative delivery system. Consequently, HA decorated nanocarriers were discussed above to improve CT or any therapeutic agent penetration over nasal mucosa,

distribution, controlled release characteristics, and specific Brain targeting.

Conclusion

Alzheimer's disease represents the main health issue that the community and health organizations must manage effectively because it has a significant negative impact on the patient's daily life and costs individuals, families, and society a lot of money. This problem worsens with the increase of the aged people. Citicoline is a form of vitamin B choline, which is considered a valued coadjutant therapy in cognitive decline in the chronic degenerative of the central nervous system diseases, including AD and Parkinson's disease-related dementia.

Currently, the majority of FDA-approved drugs for AD focus on symptomatic issues and halt or slow disease development. The marketed delivery systems of AD drugs are not well optimized. They represent oral formulae that require high doses with a succeeding high occurrence of side effects. Nanocarriers, including liposomes and SLNs, with their developed forms, are proved successful profiles in terms of efficacy and safety .

Intranasal administration of drugs to the CNS is a non-invasive strategy that avoids the BBB and reduces systemic exposure and adverse effects. Both healthy adults and people with AD have benefited from the usage of this unique technique to enhance memory. Additionally, the developed CT-loaded nanocarrier, which is decorated with HA overcame the two main barriers posed by CT (high hydrophilicity and fast metabolism), which prevent intact molecules from traversing the BBB. Through intranasal administration, the medication was efficiently and quickly delivered to the brain because of the tailored CT. Despite these encouraging results, only a small number of flexible vesicles have reached clinics due to a number of challenges associated with the high cost of manufacturing nanoparticles on a large scale and the lack of standardization protocols. In some circumstances, low colloidal stability, easy lipid peroxidation, a small loading capacity, unpredictable drug release, and other in vitro/in vivo difficulties are additional drawbacks of nanoparticles .

This emphasizes how crucial it is to focus future research on removing these obstacles and facilitating straightforward clinical translation of the most potential nanocarriers, which improve the therapeutic effect of CT and other therapeutics agent. Nevertheless, further toxicity and safety studies are required to prove these findings and support clinical experiments. Because of the technological boost in AD diagnosis, early diagnosis can help better control the disease. In conclusion, further studies are carried out for medication to prevent AD, which, if discovered, will definitely use the optimal delivery systems to reach the brain, the most protected target. In order to better manage AD, this review encourages to develop of Citicoline-loaded nanocarriers decorate with HA for effective brain delivery via the intranasal route.

Declaration of interest

The authors affirm no conflicts of interest.

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