Carbohydrate Polymer Technologies and Applications 7 (2024) 100460

Contents lists available at ScienceDirect

Carbohydrate Polymer Technologies and Applications

journal homepage: www.sciencedirect.com/journal/carbohydrate-polymer-technologies-and-applications

Chitosan – An alternative drug delivery approach for neurodegenerative diseases

Mahalaxmi Iyer [a,b], Ajay Elangovan [c], Ramya Sennimalai [d,e], Harysh Winster Suresh Babu [c], Saranya Thiruvenkataswamy [e,f], Jayalakshmi Krishnan [g], Mukesh Kumar Yadav [a], Abilash Valsala Gopalakrishnan [h], Arul Narayanasamy [e], Balachandar Vellingiri [c,*]

[a] Department of Microbiology, School of Basic Sciences, Central University of Punjab, Bathinda - 151401, Punjab, India
[b] Department of Biotechnology, Karpagam Academy of Higher Education (Deemed to be University), Coimbatore 641021, India
[c] Human Cytogenetics and Stem Cell Laboratory, Department of Zoology, School of Basic Sciences, Central University of Punjab, Bathinda, Punjab 151401, India
[d] Department of Zoology, PSGR Krishnammal College for Women, Coimbatore, Tamil Nadu 641004, India
[e] Disease Proteomics Laboratory, Department of Zoology, Bharathiar University, Coimbatore, Tamil Nadu 641 046, India
[f] Department of Zoology (PG-SF), PSG college of arts and science, Coimbatore, Tamil Nadu 641014, India
[g] Department of Biotechnology, Central University of Tamil Nadu, Thiruvarur, Tamil Nadu 610001, India
[h] Department of Biomedical Sciences, School of Biosciences and Technology, VIT, Vellore, Tamil Nadu 632014, India

ARTICLE INFO

Keywords:
Chitosan
Neurodegenerative diseases
Carbohydrate polymers
Therapeutic approach
Nanotechnology

ABSTRACT

Neurological disorders have become severe and dreadful issues around the globe that are rarely directly mediated because of the blood-brain barrier (BBB). Despite the various therapeutic strategies, including the utilization of cholinesterase inhibitors, metal chelators, molecular chaperones, and anti-body treatment that have been put forth, drug delivery to the brain has remained a problem in the treatment of neurodegenerative disorders (NDD). Chitosan, one of nature's multifunctional polymers, is acknowledged as a useful chemical in the medical and pharmaceutical industries due to its distinctive and flexible biological characteristics. By using Chitosan and its derivatives as drug delivery methods, it is possible to give medications in a sustained and regulated way, increase their stability, and lessen the likelihood of adverse drug reactions. In the current review, we have concentrated on the significance of Chitosan and its derivatives to become a hotspot in drug delivery, particularly for NDDs. This review also explains their properties as drug delivery vectors and their ability to cross the BBB, which is a significant obstacle to medication administration in NDDs. In conclusion, this review suggests that expanding the scope of such research would make it possible to develop NDD drug delivery systems that are more efficient.

1. Introduction

Polymeric drug delivery systems have advanced significantly over the past 20 years. The therapeutic approaches should be both neuroprotective and neurorestorative to delay, reverse, or prevent the disease's course (Dhivya & Balachandar, 2017). However, the disease progression is unaffected by the currently available treatment options, including pharmacological interventions and neurosurgical procedures (Xue et al., 2020). Because nanoparticles can easily cross the blood-brain barrier (BBB), they are more effective than current therapeutics for treating neurodegenerative diseases (Dong, 2018). Nanoparticle-mediated medication distribution to the brain has shown much promise in avoiding BBB obstruction (Hersh et al., 2022). To make polymeric drug delivery systems more effective the natural use of polymers like arginine, Chitosan, dextrin, poly (glycolic acid), poly (lactic acid), and hyaluronic acid has to be increased widely (Sung & Kim, 2020). Polysaccharides are a preferred base for customized pharmaceutical delivery systems because, as natural biomaterials, they (i) are widely available and relatively cheap; (ii) possess excellent biocompatibility and biodegradability; and (iii) are nontoxic and non-reactogenic (Barclay et al., 2019). In addition to techniques for discovering new drug compounds, the creation of multifunctional drug delivery systems has recently emerged as a fashionable and alluring idea in pharmaceutical science. Pharmaceutical drug carriers based on carbohydrates have shown promise to reduce dose frequency, enhance drug pharmacological action, and deliver medications to the intended place.

* Corresponding author.
E-mail address: balachandar.vellingiri@cup.edu.in (B. Vellingiri).

https://doi.org/10.1016/j.carpta.2024.100460

Available online 15 February 2024

One fascinating poly-based compound is Chitosan, a cationic polysaccharide consisting of D-glucosamine and N-acetyl-D-glucosamine units randomly distributed throughout its structure, posing chelating qualities. It is made by deacetylating Chitin, a carbohydrate found in crab shells (Huang et al., 2017). It is naturally seen as organized microfibrils in the cuticles of fungi and insects and the exoskeletons of mollusks and crustaceans (Kaur & Dhillon, 2014). Demineralization, deproteinization, and decolorization are all sequential steps involved in the technique for chitin extraction from shellfish wastes in the industry (Beaney et al., 2005; Shahidi & Synowiecki, 2002). Chitosan has garnered interest as a nontoxic, secure, and promising agent for use in drug delivery systems. Many experiments have recently been conducted to create medication delivery systems employing Chitosan to treat neurological illnesses (Shayganfard, 2022). This review article emphasizes chitosan-based biopolymers as a helpful drug delivery method for NDDs. The primary purposes of Chitosan are highlighted and discussed in this study, along with the restrictions placed on nanoparticle-based drug release systems, the most prevalent NDD, and current developments in the micro/nanoparticulate chitosan-based drug delivery systems.

2. Neurodegenerative disease – an overview

Neurodegenerative diseases (NDD) illnesses emerge when neurons in the spinal cord and brain begin to age. Neurodegeneration has been recognized as the main pathological change in most diseases affecting the brain. The major challenge in the treatment of NDD is the inability of pharmaceuticals to cross the BBB and reach the target tissue. The BBB showcases a high degree of selective permeability (Chowdhury et al., 2017; Vellingiri et al., 2022). Large, non-lipophilic compounds with high polarities are prevented from passing through this barrier, which gives rise to the need to use carriers for the delivery of drugs. Therefore, synthesizing chitosan-based efficient carriers for drug delivery is the upcoming area of research. (Patel & Patel, 2017). The NDDs, which include conditions such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD), are among the most crippling age-related conditions in people (Balachandar et al., 2012; Hou et al., 2019; Venkatesan et al., 2021; Venugopal et al., 2018), almost 6.3 % of the global burden of all diseases is attributable to NDDs (Misra et al., 2003). Despite adequate blood flow, the transport of medications through the central nervous system is a significant issue. The blood-cerebrospinal fluid barrier (BCSFB) and the BBB, two physiological obstacles, isolate the brain from its blood supply. Minimal strategies are available for NDDs-related therapeutics and treatment because of the highly selective permeability of BBB. Out of which, drug delivery into the CNS is one of the most challenging problems faced. (Barchet & Amiji, 2009). Earlier surgeries and highly evasive, classical techniques were used for treatment and drug delivery. However, their long-term benefit was a matter of concern because of the potential damage to the brain it causes, as well as the local administration of drugs with the inability to diffuse to other parts of the brain. Nanotherapeutics that can cross the BBB non-invasively have been proposed and shown in several circumstances as a feasible alternative for slowing or reversing neurodegeneration (Harilal et al., 2019; Hinge et al., 2022). Nanocarriers such as liposomes, solid-lipid nanoparticles, nanoemulsions, and polymeric nanoparticles are some examples of potential nano techniques that can be used for therapeutic purposes (Barchet & Amiji, 2009). In addition to techniques for discovering new drug compounds, the creation of multifunctional drug delivery systems has recently emerged as a fashionable and alluring idea in pharmaceutical science (Mukherjee et al., 2022). Pharmaceutical drug carriers based on carbohydrates hold promise since they can deliver pharmaceuticals at the desired spot, improve drug pharmacological activity, and reduce the doses needed (Agnihotri et al., 2004; Akhtar et al., 2021). Chitosan is employed as a matrix to mediate the transfer of doxycycline hydrochloride across the BBB, according to Yadav et al.'s 2017 research (Yadav et al., 2017). Chitosan is a fantastic option for biomedical applications because of its bioavailability and biodegradability (de Oliveira Pedro et al., 2018; M. Ways et al., 2018). It is an appropriate matrix that will give the drug's encapsulation a solid foundation (Dhanavel et al., 2017). Therefore, these studies demonstrate that Chitosan is a potential new therapeutic option for neurological disorders as a promising intravenous neural drug discovery.

3. Existing therapeutic approaches for NDD

A lot of time and effort are still needed to develop a drug that can treat neurodegenerative illnesses because it is such a massive undertaking. Therefore, the requirements for an effective treatment will only be discussed in part.

3.1. Silibinin treatment

Several models of neurodegenerative disorders have demonstrated the neuroprotective effects of the natural flavonoid silibinin. This study sought to determine how silibinin affects memory loss and oxidative stress from mice's amyloid β (Aβ) peptide. The administration of silibinin was reported to counteract memory impairment brought on by Aβ peptide, as seen by improved performance in the passive avoidance test and the Morris water maze test. A decrease in oxidative stress markers in the brain further demonstrated that silibinin therapy lessened the oxidative stress brought on by the Aβ. According to these results, silibinin may be able to treat NDD conditions allied with memory loss and oxidative stress (Lu et al., 2009).

3.2. Curcumin treatment

According to Reddy et al.'s 2017 evaluation, curcumin treatment significantly improved memory and cognitive function in animal models of AD. Due to curcumin's ability to reduce amyloid-beta levels and tau hyperphosphorylation, cognitive function was improved. Additionally, this result was brought about by its anti-inflammatory and antioxidant properties. An increase in the expression of synaptic plasticity-related proteins, such as PSD-95 (postsynaptic density protein-95) and synaptophysin, was also seen after curcumin administration (Reddy et al., 2018).

3.3. Quercetin and quercetin-3-β-d-glucoside treatment

In an *in vivo* model of AD that involves the intracerebroventricular injection of amyloid β (Aβ25–35), Kim et al.'s 2016 study assessed the preventive effects of two flavonoids, quercetin (Q) and quercetin-3-D-glucoside (Q3G). According to our research, Q and Q3G enhanced cognitive and memory skills compared to the control group, which received an amyloid β (Aβ25–35) injection. The administration of Q and Q3G significantly reduced the amount of lipid peroxidation and NO (nitric oxide) production in the brain after Aβ25–35injection in control mice. Therefore, this study implies that Q and Q3G may have the ability to improve memory deficits and cognitive impairment brought on by Aβ25–35, as well as provide neuroprotection against oxidative stress in the brain (Kim et al., 2016).

3.4. Nobiletin treatment

Nakajima et al. (2015) have shown the natural substance nobiletin to improve cognitive performance while simultaneously lowering soluble Aβ levels in the triple transgenic mice model of AD (3XTg-AD). This approach gradually produces amyloid plaques, neurofibrillary tangles, and cognitive impairment. The short-term and recognition memory deficits experienced by those with 3XTg-AD were reversed in these mice after three months of receiving a nobiletin dosage of 30 mg/kg. Additionally, ELISA research revealed that nobiletin decreased the

concentrations of soluble Aβ−1–40 in the brains of the 3XTg-AD mice. When given nobiletin, it has also reduced ROS levels, indicating that the natural substance may one day be used as a new medication to prevent and treat AD (Nakajima et al., 2015).

3.5. Novel curcumin formulation treatment

Curcumin has better cellular absorption, and the data showed that NCF was safer and more effective than the CUR control. Based on these evaluations, it was determined that NCF outperformed currently existing treatment alternatives by not only halting the decline of the elderly mice's cognitive functions but also turning them around to a more youthful state. After conducting a thorough safety examination, it was determined that NCF was well tolerated and had no adverse effects (Parikh et al., 2018).

3.6. Perilla frutescens var. japonica and rosmarinic acid treatment

In the T-maze and object recognition tests, Lee et al. (2016) study found that giving PFE (*Perilla frutescens* var. *japonica* extract) and RA (rosmarinic acid) significantly enhanced cognitive performance and study object discrimination while also offsetting the unfavorable effects caused by Aβ25–35. Nitric oxide (NO) and malondialdehyde (MDA) levels in the brain, liver, and kidney were also decreased after receiving PFE and RA. Notably, PFE substantially reduced oxidative stress by preventing the generation of NO and MDA in the mouse brain after Aβ25–35 injection (Lee et al., 2016).

3.7. Grewia asiatica berry juice

According to Imran et al. (2021) study from 2021, the behavior of rats given 20 % and 30 % dilutions of fruit exudate was significantly affected. In the T mazes of the open field test, two popular anxiety tests, these animals displayed anxiolytic behavior. Additionally, in the forced swim test, rats who were given a higher concentration of exudate showed decreased immobility, which is a sign of antidepressant-like action. As evidenced by improved cognitive performance in numerous tests, medicated rats in learning and memory experiments showed that the effects of scopolamine-induced amnesia could be reversed. Superoxide dismutase and glutathione peroxidase levels in the isolated brains of treated rats showed a considerable rise ($P < 0.05$), while acetylcholinesterase and malondialdehyde levels showed a significant decrease ($P < 0.05$). These outcomes indicate that this fruit exudate has medicinal potential.

3.8. Rutin treatment

Rutin, a naturally occurring flavonoid glycoside, inhibited tau aggregation and tau oligomer-induced cytotoxicity *In vitro*. It also decreased the release of pro-inflammatory cytokines and preserved neuronal shape. Significantly, rutin promoted extracellular tau oligomer uptake by microglia. Rutin therapy decreased pathogenic tau levels, controlled tau hyperphosphorylation, and inhibited gliosis and neuroinflammation in Tau-P301S animal models of tauopathy. Rutin also repaired synapse loss, inhibited microglial synapse engulfment, and markedly enhanced cognition. Rutin compounds constitute a viable pharmacological candidate for combinatorial targeting of tau and Aβ in treating AD (Sun et al., 2021).

3.9. Naringin treatment

Naringin can dramatically enhance cognitive, learning, and memory skills in mice with hydrocortisone-induced memory impairment, and it is evident that naringin, having neuroprotective properties, can significantly improve cognitive function in mice with memory impairment. As a result, naringin has considerable promise as a potential candidate for a particular drug to treat AD (Meng et al., 2021).

3.10. Safflower seed extract treatment

Kim et al. (2019) study shows that after 100 mg/kg/day of sunflower seed extract was administered, several behavioral tests, including the T-maze and novel object recognition tests, were carried out. Analyses of the acetylcholinesterase (AChE) activity, reactive oxygen species (ROS) generation, and antioxidant enzymes in the brain were carried out to evaluate the efficacy of safflower seed extract. According to the results, the injection of safflower seed extract appeared to improve item recognition and innovative route exploration, which implies that memory function is enhanced by safflower seed extract in a scopolamine-treated mouse model. Safflower seed extract recipients also showed reduced cholinergic dysfunction and decreased AChE activity.

3.11. Coffee polyphenol treatment

APP/PS2 transgenic mice were given a diet containing 0.1 % coffee polyphenols for six months. A contextual fear conditioning test was performed to measure cognitive function, and immunohistochemical analysis was employed to determine Aβ pathology. According to our findings, coffee polyphenols shielded APP/PS2 mice's brains from A plaques and avoided cognitive impairment. Additionally, coffee polyphenols decreased the concentrations of soluble Aβ in the brain by preventing the action of β-secretase, a crucial enzyme in the synthesis of Aβ. So, according to our research, coffee polyphenols have a high therapeutic potential for reducing AD cognitive symptoms (Ishida et al., 2020).

3.12. Phosphodiesterase-4 (PDE4) treatment

The Morris water maze and novel object recognition tests revealed a considerable cognitive decline in the APPswe/PS1dE9 mice, which the oral administration of roflumilast successfully reversed at 5 and 10 mg/kg per day. The tail-suspension test and the forced swimming test likewise revealed prolonged immobility time in the AD mice, which roflumilast was able to reduce. Roflumilast was shown to lessen neuronal cell damage by hematoxylin-eosin and Nissl staining, and it was also shown to decrease cell apoptosis in AD mice by terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick-end labeling analysis (Wang et al., 2020).

3.13. Paeoniflorin (PF) treatment

In a 2018 study by Wang et al. (2018), the possible neuroprotective effects of Paeoniflorin (PF) were investigated regarding cognitive deficits brought on by STZ intracerebroventricular (ICV) injection in mice. On days 1 and 3, 3 mg/kg of STZ was injected into the ICV twice on alternate days. Following the start of STZ treatment, daily PF (10 mg/kg) intraperitoneal administration for 21 days significantly improved the cognitive deficits caused by ICV-STZ as measured by the Morris water maze (MWM) test and novel object recognition test. Additionally, PF administration significantly reduced oxidative stress and STZ-induced mitochondrial dysfunction in the cortex and hippocampus compared to the control group, as evidenced by increased cytochrome c oxidase activity, ATP synthesis, and restoration of the mitochondrial membrane potential (MMP). The findings of this study imply that PF may be used to treat the cognitive deficits brought on by ICV-STZ when taken as a whole .

3.14. Lutein treatment

According to the study by Nazari et al. (2022), passive avoidance testing and the Morris water maze were used to assess the cognitive ability of rats. The study showed that lutein supplementation had a

protective effect on learning and memory in the AD rat model, enabling improved performance in the behavioral tests. Lutein has the potential to be an effective treatment for AD, and more study is needed to understand its mechanism of action works (Nazari et al., 2022).

3.15. Tannic acid treatment

In 2022, evidence from Ullah et al. (2022) showed that tannic acid (TA) and lipopolysaccharide were administered to adult male mice once and twice weekly during the three-month trial. Western blotting and immunofluorescence labeling methods examined the protein expression of particular mediators, including TNF-α, p-JNK, pIRS636, BACE1, APP, and Aβ. Biochemical experiments were carried out to gauge TA's antioxidant properties. A computer analysis was also done to examine how TA binds to TNF- α target sites. The findings of the behavioral tests showed that the mice treated with TA had better memory. TA dramatically reduced the activity of BACE1, resulting in less A synthesis and accumulation in the mouse brain's hippocampus. Additionally, TA significantly increased glutathione levels while reducing LPS-induced ROS generation. All the studies are described in the form of Table 1.

All the above-mentioned therapeutic modules for AD with phytochemicals can delay the onset of AD and slow its progression. Some can promote the recovery of damaged neuronal cells by targeting various pathogenic pathways with their anti-cholinergic, anti-inflammatory, and antioxidant properties. Also, low bioavailability of the drug, limited transport, and long-term effects of the drug over the system pose a significant threat to using traditional drugs for the treatment of AD. At the same time, using chitosan nanoparticles can increase the loaded drug's bioavailability and provide a multifunctional platform that can aid in various theragnostic applications.

4. Current clinical trials for NDD

Clinical trials are scientific investigations that put a medical, surgical, or behavioral intervention before human subjects. These studies are the primary means by which scientists ascertain the safety and efficacy of new forms of therapy or prevention, such as new drugs, diets, or medical devices, in humans. There are several chances for failure in clinical trials for drugs and medical devices. From preclinical to phase 3, the resources, time, and financial commitments increase with each stage (Fogel, 2018).

Parkinson's disease (PD) and dementia of the Alzheimer's type, two

Table 1
Therapeutic approaches for NDD.

S. No	Treatment	Dosage	Model	Country	Major findings	Refs.
1.	Silibinin treatment	1 mg/ml	Male ICR mice	Japan	↑ Memory impairment ↓ ROS ↓ Activation of microglia ↓ TNF-α & IL-1β	Lu et al. (2009)
2.	Curcumin treatment	3–30 mg/kg	Mouse models of AD	Lubbock	↑ Cognitive function and memory ↓ Amyloid-beta levels and tau hyperphosphorylation ↑ Cognitive function ↑ PSD-95 & synaptophysin	Reddy et al. (2018)
3.	Quercetin and quercetin-3-β-D-glucoside treatment	30 mg/kg	Mice	Korea	↑ Cognitive and memory skills ↓ Oxidative stress	Kim et al. (2016)
4.	Nobiletin treatment	10or 30 mg/kg	Homozygous 3XTg-AD and non-transgenic wild-type mice	USA	↑ Cognitive performance ↓ Aβ ↓ ROS	Nakajima et al. (2015)
5.	Novel Curcumin Formulation treatment	47 mg/kg −150 mg/kg	Male Sprague-Dawley rats	South Australia	↑ Cognitive performance	Parikh et al. (2018)
6.	*Perilla frutescens* var. *Japonica* and rosmarinic acid treatment	50 mg/kg & 0.25 mg/kg	Male ICR mice	Korea	↑ Cognitive function ↓ NO & MDA ↓ OS	Lee et al. (2016)
7.	Grewia asiatica Berry Juice	2 mg/kg	Sprague-Dawley (SD) male rats	Multan	↓ Immobility ↑ Cognitive performance ↑ Superoxide dismutase & glutathione peroxidase ↓ Acetylcholinesterase & malondialdehyde	Imran et al. (2021)
8.	Rutin treatment	100 mg/kg	Six-month-old male Tau-P301S mice	China	↓ Gliosis ↓ Neuroinflammation ↓ tau and Aβ	Sun et al. (2021)
9.	Naringin treatment	30 mg/kg	Male mice	China	↑Neuroprotective action ↑ Memory	(Meng et al., 2021)
10.	Safflower seed extract treatment	100 mg/kg	Male ICR mice	Korea	↑ Memory function ↓ AChE activity ↓ ROS generation ↑ Antioxidant enzymes	Kim et al. (2019)
11.	Coffee polyphenol treatment	CPP diet	APP/PS2 double transgenic mice and wild-type (WT) littermates	USA	↓ Aβ plaques	(Ishida et al., 2020)
12.	Phosphodiesterase-4 (PDE4) treatment	5–10 mg/kg	APP/PS1 double transgenic mice	China	↓ B-cell lymphoma-2/Bcl-2-associated X ↓ cyclic AMP (cAMP	Wang et al. (2020)
13.	Paeoniflorin (PF) treatment	10 mg/kg	C57BL/6 mice	China	↓ Oxidative stress ↑ p-PI3K ↑ p-Akt ↓ p-IRS-1	Wang et al. (2018)
14.	Lutein treatment	5 mg/kg	Wister rat	Iran	↑ Learning ↑ Memory	Nazari et al. (2022)
15.	Tannic acid treatment	30 mg/kg	Male Balb/c albino	UK	↓ BACE1 ↑ ROS	Ullah et al. (2022)

neurodegenerative diseases whose incidence rises with advancing age, will soon place a heavy burden on societies that, like our own, are aging. Since most neurodegenerative disorders' etiology and pathophysiology are unknown, they pose a research challenge. It is challenging but vital to create cures for diseases whose causes are currently unknown (Jayaramayya et al., 2020; Stanzione & Tropepi, 2011). Clinical trials for neurodegenerative illnesses necessitate the long-term monitoring of a large number of patients, making it difficult to continue the studies and driving up expenditures. Additionally, only a few symptomatic therapies are accessible due to the abysmal success rate, and therapeutic drugs able to slow the progression of the disease have not yet been created. Alternative study designs may prove valuable in finding disease-modifying therapies because research must continue while waiting for the pathways underlying neurodegeneration to be exposed (Iyer et al., 2016; Reddy et al., 2020). For each neurological condition across all Indian states in 2019, they provide general, age, and sex-specific prevalence or incidence rates and disability-adjusted life years (DALY) rates. The 2019 deaths in India are included for each neurological ailment. All non-communicable neurological illnesses, except stroke, are reported for their prevalence.

In contrast, stroke, infectious neurological disorders, and injury-related neurological disorders are noted for their incidence, according to the metric that is most frequently applied clinically for each condition. The research on the Global Burden of Diseases (GBD) and global neurological disorders, which was previously published, also employed the same measures. It is impossible to compare the prevalence and incidence directly (Singh et al., 2021, pp. 1990–2019). The Current Clinical Trial Data was collected from "ClinicalTrials.gov," a resource provided by the U.S. National Library of Medicine that will be available worldwide. Table 2 demonstrates the details of Current clinical trials in neurodevelopmental diseases.

Table 2
Current clinical trials for NDD.

S. NO	AD/PD	Sample Size/ participants	Study starting Year	Study Ending Year	Drug/ Device/Work	Country	Status
1.	PD	500	2020	2023	Harmane (HA) and essential tremor (ET)	United States	Recruiting
2.	AD & PD	10,000	2019	2029	Diagnostic Test: Boston Cognitive Assessment (BoCA)	United States	Recruiting
3.	PD	200	2016	2023	Analyze of Mild Cognitive Impairment	Canada	Recruiting
4.	PD	450	2020	2024	Drug: UCB0599 Drug: Placebo	United States	Active, not recruiting
5.	AD	1800	2020	2025	Drug: Donanemab Drug: Placebo	United States	Active, not recruiting
6.	Neurodegenerative diseases	150	2020	2023	Radiation, Magnetic Resonance (MR) and positron emission tomograph (PET) imaging analyses	Italy	Recruiting
7.	AD	1083	2021	2024	Drug: Simufilam Drug: Placebo	United States	Recruiting
8.	Neuro-Degenerative Disease	250	2017	2024	Other: fMRI	Canada	Recruiting
9.	PD	4500	2020	2033	PPMI 2.0	United States	Recruiting
10.	AD& PD	60	2019	2023	Drug: Placebo oral capsule Drug: Nilotinib Oral Capsule	United States	Recruiting
11.	Neurodegenerative Disorders	50	2021	2024	Drug: 18F-T807	China	Recruiting
12.	AD & PD	534	2021	2023	Device: TeNDER tool	Spain	Recruiting
13.	PD	08	2022	2027	Biological: STEM-PD	Sweden & UK	Recruiting
14.	PD	30	2021	2029	Video-oculography / Neuropsychological evaluations	Monaco	Recruiting
15.	AD & PD	245	2016	2024	Pittsburgh Compound B [11C]-PIB	Canada	Recruiting
16.	AD & PD	136	2021	2027	Drug: 11C-MC1 Drug: 11C-PS13 Drug: 18f-florbetaben	United States	Recruiting
17.	AD & PD	355	2023	2024	Behavioural: Algorithm Behavioural: Random Match	United States	Recruiting
18.	AD & PD	10,000	2010	2030	Lumbar punction	France	Recruiting
19.	PD	316	2017	2026	Drug: RO7046015 Drug: Placebo	United States	Active, not recruiting
20.	AD	6000	2020	2025	Body Fluid, Gene and Neuroimaging Biomarkers for Early Diagnosis of Alzheimer's Disease	China	Recruiting
21.	AD & PD	1505	2017	2028	Diagnostic Test: Flutemetamol F18 Injection Diagnostic Test: [18F]-RO6958948 Diagnostic Test: Elecsys (Roche) Abeta42, Ttau and Ptau Diagnostic Test: Lumipulse (Fujirebio) Abeta42, Ttau and Ptau	Sweden	Recruiting
22.	AD & PD	76	2018	2023	Radiation: DaTscan Radiation: F18-AV-45 Radiation: FDG-PET Genetic: APOE genotype Procedure: Polysomnogram Behavioral: Clinical Assessment	United States	Recruiting
23.	AD	1000	2017	2025	Retinal Imaging	United States	Recruiting
24.	AD	80	2017	2024	tDCS	France	Recruiting
25.	AD	300	2019	2023	Drug: F-18-AV45	Taiwan	Recruiting

5. Carbohydrate bio-polymers – a novel therapeutic approach for NDD

Biopolymers are extensively eco-friendly since they are biodegradable & biocompatible and are accentuated in various biomedical applications (Azeem et al., 2017; Torres et al., 2019; Wei et al., 2021). These biopolymers are used in multiple aspects of neurodegeneration and have been proven to have a positive effect.

5.1. Polyphenols

Polyphenols have an essential function, such as acting as a defense against the accumulation and attack of pathogens, and it is proved that the use of food substances that are polyphenol-rich could deliver fortification counter to neurodegenerative disorders (Graf et al., 2005). Flavonoids are a form of polyphenols that can be used against inflammatory disorders and are involved in treating Alzheimer's Disease (AD) and Parkinson's Disease (Widhiantara et al., 2021). Flavonoids, with antioxidants, prevent oxidative stress damage of a cell. Flavonoids have also been associated with inhibiting inflammatory cytokines such as IL-1, TNF-α, and IL-6, which ultimately protect neuronal cells by inhibiting the triggering of microglial cells in the case of PD. By inhibiting Ca^{2+}ATPase, flavonoids exert their therapeutic effects in AD (Shukla et al., 2019). Resveratrol, another polyphenol biopolymer, has an extensive impact on AD treatment by decreasing factors of proinflammation (NF-kB pathway) and regulating various pathways of autophagy (Dhingra et al., 2021).

5.2. Alginate

Alginate is an oligosaccharide biopolymer that possesses antioxidant effects. It has the potential to upregulate the levels of GSH (Glutathione), thereby mediating the cellular OS and protecting the neuronal cell death induced by H_2O_2 (Eftekharzadeh et al., 2010), which is a depository product in AD and regulates NF-kB pathway insisting on its neuroprotective effect in AD.

5.3. Glycan

Glycans are prime in various cellular functions, such as disease progression. Anomalous glycation and glycosylation in NDDs result in protein dysfunction and aberrant deposition. Hence, the modulation of glycosylation can be used as a therapeutic approach against protein deposition in neurodegenerative disorders, and the intonation is done via modulating the regulator enzymes such as glycosidases and glycosyltransferases (Esko et al., 2015). The various functions of biopolymers of carbohydrates are explained in Fig. 1.

5.4. Polysaccharide fractionate

Damage to the nerve cells induced due to the upregulated concentrations of excitatory amino acids by the undue stimulation of glutamate receptors is called excitotoxicity. Lemieszek et al. (2018) have demonstrated the activities of polysaccharide fractions from C. cibarius have a neuroprotective effect and protect the neuronal cells against excitotoxicity (Lemieszek et al., 2018). Similarly, polysaccharides from T. fuciformis yielded the same result as a neuroprotectant (Jin et al., 2016). In PC12 cells, the polysaccharides from C. cicadae had a neuroprotective effect against glutamate-induced damage (Olatunji et al., 2016).

6. Chitosan – a carbohydrate bio-polymer

Chitosan is a deacetylated chitin derivative comprising N-acetyl-D-glucosamine and D-glucosamine (Kumar et al., 2004; Zargar et al., 2015). The Chitin can be extracted from various sources such as fungi, crustaceans, worms, yeasts, and mollusks (Anitha et al., 2014; Bo et al.,

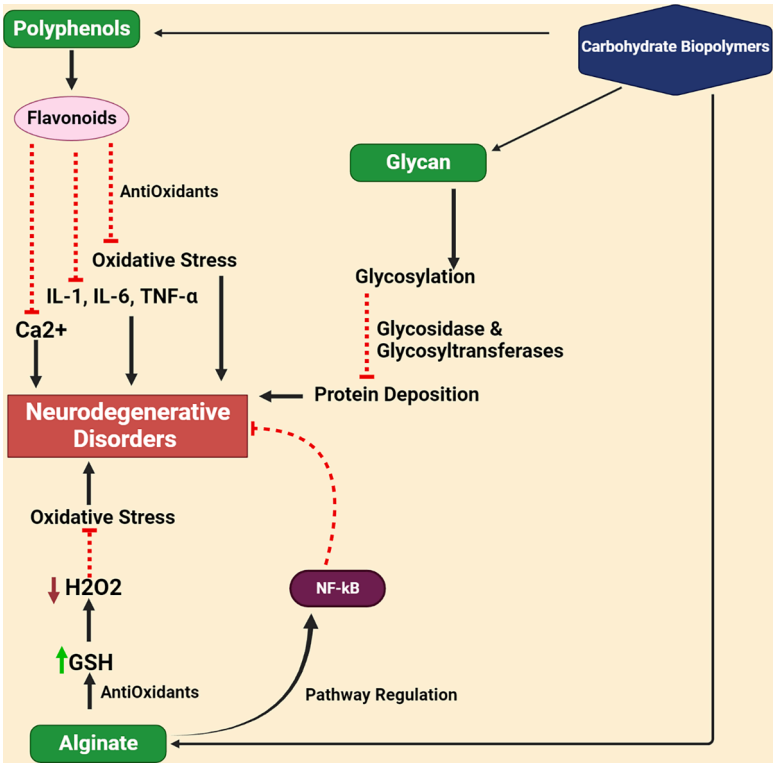

Fig. 1. Chitosan the suitable carbohydrate polymers - The functions of carbohydrate biopolymers towards neuroprotection in neurodegeneration via its variants such as polyphenols, glycans and alginate has been explained. Polyphenols has flavonoids which protects the cells against OS, inflammatory cytokines and excitotoxicity. Alginate upregulates GSH which in turn downregulates hydrogen peroxide production protecting against OS. Glycan clears protein deposition by glycosylation using enzymes such as glycosidase and glycosyltransferase.

2012; Ehrlich et al., 2010; Wysokowski et al., 2015). Recently, researchers have initiated to acknowledge Chitosan as a biomedically useful biopolymer that is biodegradable & renewable, functional, and nontoxic. have the potential usage in several fields such as food (Shahidi & Synowiecki, 2002), pharmaceutics, and cosmetics (Zhang et al., 2010; Li et al., 2018). Chitosan also possesses antimicrobial, immunoenhancing, and antitumor properties (Bellich et al., 2016). Chitosan and its derivatives exert neuroprotective roles and are classified into some mechanisms, namely Anti-Apoptosis, Anti- Neuroinflammatory, Anti-Excitotoxic, Clamping down the aggregation of Aβ and Suppressing the action of Oxidative stress.

6.1. Anti-apoptosis

Chitosan (CS) is proven to have properties that suggestively increase the viability of cells and decrease the release of LDH (Lactate dehydrogenase) (Wang et al., 2016). In the cell apoptosis induced by DBT (Dibutyltin), the disturbance of MMP (Mitochondrial membrane potential) and ROS production were diminished by CS (Wang et al., 2016). Another study by Koo et al. (2002) demonstrated that CS inhibits neuronal and astrocyte cell death via the blockage of glutamate receptors (Koo et al., 2002).

6.2. Anti-Inflammatory

Neuroinflammation plays a prime role in neurodegeneration, which is mediated by the release of inflammatory cytokines (Elangovan et al., 2023). Kim et al. (2002) found that in astrocytoma cells of humans, water-soluble CS could constrain the pro-inflammatory cytokine production triggered by IL (Interleukins) and Aβ. Pre-treatment of CS in astrocytoma cells of humans significantly inhibits the expression of IL-6, TNF-α, and iNOS (inducible nitric oxide synthase) (Kim et al., 2002).

6.3. Anti-excitotoxic

As explained in the previous topics, the glutamate and glutamate receptors play a significant role in the physiology of neurodegeneration. One of the products of Chitosan, COS (Chito oligosaccharides), protects hippocampal neuronal cells against apoptosis due to glutamate. COS downregulates the concentration of calcium $Ca^{2+}$and provokes glutamate-induced caspase-3 activation (Zhou et al., 2008).

6.4. Clamping down the aggregation of Aβ

Aβ peptide plaque formation is a chief concern in AD (Elangovan et al., 2023; Sasikalaa et al., 2016). In a study done by Dai et al. (2013), they discovered that COS might possess fibrillogenic properties against Aβ plaque formation, and treatment of cells with COS protects the cells against Aβ deposition and generation ROS (Dai et al., 2013). By blocking the ability of the BACE-1 gene, COS delivers a neuroprotective effect that results in downregulated Aβ deposition (Byun et al., 2005; Je & Kim, 2005).

6.5. Suppressing oxidative stress

It is a known fact that free OS is present in most neurodegenerative diseases and plays a prominent role in cell death, which is mediated by free radicals (Fenn et al., 2016). Consequently, regulating free radicals allows the OS to be controlled or managed in neurodegenerative disorders. Hao et al. (2015) experiment on PC12 cells showed that PACO (Peracetylated chitosan oligosaccharides) reduces LDH and ROS. Additional studies suggested that PACO protects cells against death by glutamate via downregulating the ratio Bax/Bcl-2 and activation of caspase-3 (Hao et al., 2015), indicating the potential of chitosan derivatives against OS in neurodegenerative disorders.

Chitosan and its derivatives play a pivotal role in various aspects of neuroprotection, as explained in Fig. 2.

7. Chitosan – available sources and extraction methods

Chitosan is a linear copolymer obtained from the deacetylation of polysaccharide chitin (Dodane & Vilivalam, 1998). Chitin is commonly present in organisms in species like crustaceans (Cray Fish, Shrimp, squids), insects (beetles, grasshoppers, honey bees, locusts), and microorganisms (fungi, algae) (Moura et al., 2011; Muzzarelli, 1973; Pochanavanich & Suntornsuk, 2002). Various steps, including pre-treatment, Deproteination, Demineralization, Decolouration, Purification, and Deacetylation, follow the extraction of Chitosan. In the pre-treatment step, the organism's soft tissues were removed entirely and sterilized by cleaning with hot water. Then, the Chitin's biomass (shell, Exoskeleton) will be chopped or grounded and sieved in the 60–120 μm mesh, and the powder form will be taken for further processing (Mohammed et al., 2013). The obtained powder of biomass was taken for deproteination. The deproteination step will be carried out using chemical and biological methods. The chemical method (Alkaline treatment) is commonly used; here, NaOH breaks down the protein at high temperatures (Bajaj et al., 2011; Marei et al., 2016). In the biological method, *B. cereus* SV1 protease enzyme was used to digest the protein at the optimum condition (40 °C) (Manni et al., 2010). Followed by deproteination demineralization was done with the help of acids (Bastiaens et al., 2019). HCl is commonly used as a demineralizing agent to remove Calcium carbonate (CaCO3) from the exoskeletons of crustaceans and other organisms (Abdou et al., 2008; Manni et al., 2010). In the decoloration step, the pigments were removed using acetone, potassium permanganate, ethanol, and chloroform (Liu et al., 2012; Mohammed et al., 2013). After completion of the deproteination, demineralization, and decoloration, samples were washed in the deionized water to neutralize the pH, and finally, Chitin was dried and taken for the deacetylation (Bajaj et al., 2011; Manni et al., 2010; Pochanavanich & Suntornsuk, 2002). The deacetylation treatment is done to obtain the Chitosan from the Chitin. NaOH/KOH is commonly used to perform the deacetylation process. The Chitin was soluble while treated with NaOH in an alkaline condition. The solidified Chitin was maintained at a high temperature for completing the deacetylation process (Manni et al., 2010; Moura et al., 2011; Pochanavanich & Suntornsuk, 2002). Then, the samples were taken for purification, mixed with acetic acid, and centrifuged at 6650 g for 30 min to remove the insoluble particles. The NaOH was added to the supernatant to precipitate Chitosan. Finally, the precipitated Chitosan was dried and stored. The available sources and the respective extraction methods have been given in Table 3.

8. Chitosan – biological properties

Chitosan has a wide range of physicochemical properties, including a rigid structure with glucosamine residues showing an increased hydrophilic and crystalline nature. It is whitish yellow and has a higher molecular weight of 1.2×10^5 g/mol. They are linear cationic biopolymers with high nitrogen content and high charge density (one positive charge per glucosamine residue) at pH < 6.5 with excellent ionic conductivity (Zhao et al., 2018). Chitosan is insoluble in organic solvents and water while soluble in dilute hydrous acidic solutions. It can also act as a weaker base, a powerful nucleophile (pKa 6.3), and a flocculating agent. They form intermolecular hydrogen bonds with increased viscosity, density (0.18–0.33 g/cm^3), and optical clarity.

Moreover, they show film-forming, chelating, and complexing properties with high entrapment and adsorption efficacy (Muxika et al., 2017). Because of the physicochemical properties engrossed with the Chitosan, they show various biological properties, including biocompatibility, i.e., safe and nontoxic, with mucoadhesive properties and biodegradability. They show a wide spectrum of activities, including hemostatic (causes bleeding to stop), fungistatic (hinders the growth of

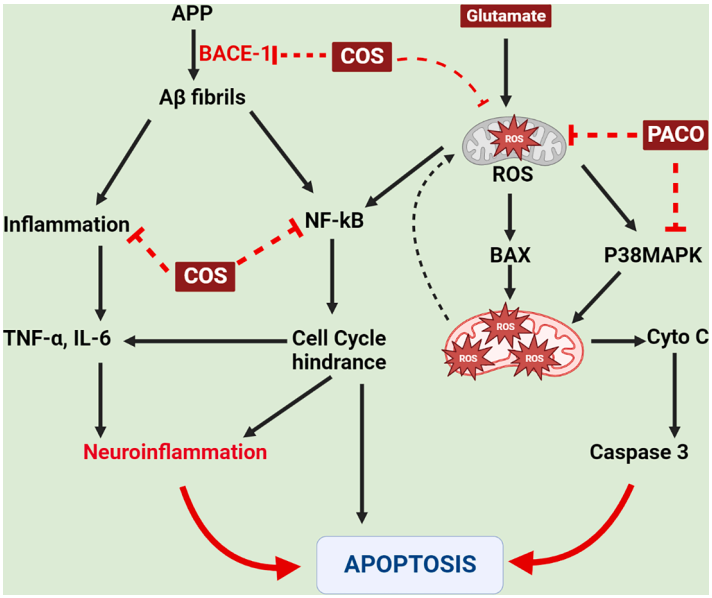

Fig. 2. Chitosan against neuronal inflammation: Depicted are the several means by which chitosan and its by-products protects a cell against many physiological reactions in neurodegeneration. This includes COS, PACO, Glutamate interfering in clearing Aβ fibril formation, NF-kB pathway regulation and neuroinflammation.

fungi), spermicidal (controls pregnancy), anti-cholesteric (lowers cholesterol level), and anticancer or antitumor (inhibits the growth of tumor cells) activities (Kołodziejska et al., 2021). It can also act as a CNS depressant (decreasing brain activity) and as an immunoadjuvant (involved in improving the immune response). They have the potency to hasten the process of osteoblast development and play a pivotal role in bone formation. Furthermore, they interact with mammalian and microbial cells, effectively showing antioxidant and antimicrobial activity. They possess wound management efficacy and aid in orthopedic and periodontal application (Aranaz et al., 2021).

9. Chitosan-based drug delivery for diseases

Chitosan-based drug delivery system is also used to treat diseases like Diabetes Mellitus apart from NDs (Revathi et al., 2023). Due to its excellent biodegradability, biocompatibility, hypoallergenic, antibacterial, immune, and antitumor activities, Chitosan has garnered considerable interest from researchers worldwide (Tang et al., 2023). The stimuli-responsive properties of chitosan hydrogels have become an active area of research since this technique may now enable the regulated release of drugs at target sites (Tian & Liu, 2023). Along with NDs, recent studies have also established the roles of N-benzyl-O-acetyl-chitosan, Imino-chitosan, Sulfated-chitosan oligosaccharides derivatives as potent antiviral candidates due to their high binding affinity of the ligands (Modak et al., 2021). Chitosan-based nanocarriers are used for anticancer drug delivery and chemotherapy (Alhodieb et al., 2022). Additionally, CS NPs are effective in several biomedical applications for the treatment of diseases (Khalaf et al., 2023).

Chitosan and its nanoform, in particular, are the most appealing natural polymers to utilize for controlled release in various drug delivery systems. Given its exceptional biocompatibility, biodegradability, and adsorption characteristics, Chitosan has been highly suggested as a good functional material (Jafernik et al., 2023). The presence of functional amino and hydroxyl groups in its structure is partially responsible for this attraction. These molecules efficiently bind to active compounds, thus rendering Chitosan to change feasibly, which is crucial for the exact dosing and prolonged release of drugs or other bioactive substances (Muxika et al., 2017). Because of their unique *in-situ* gelling abilities and mucoadhesive nature, they are utilized in administering drugs to treat eyes. Chitosan-coated nanocapsules have shown favorable eye tolerance and are an effective way to increase the ocular bioavailability of different therapeutic medications (Calvo et al., 1997). They are also utilized in oral drug delivery because they improve absorption by loosening tight mucosal membrane connections. They help deliver pulmonary drugs due to their positive charge (Garg et al., 2019). They aid in the mucosal drug delivery process by enhancing the absorption of hydrophilic compounds. It acts as an adjuvant in the administration of vaccines. It has also been proven to be successful in the treatment of cancer. The physiochemical characteristics of chitosan NPs are largely responsible for these wide applications.

Chitosan acts both as a vector for carrying the drug payload and as a therapeutic drug in its modified form (Aranaz et al., 2023). The composites formed with the Chitosan have been used to deliver medicinal drugs to the brain, i.e., crossing BBB (Rajamanickam & Manju, 2023; Yang et al., 2023) for treating cerebral hemorrhage. They can also aid in the treatment of diseases like migraine and brain cancer.

One of the composites that have played an important role in treating AD is the selenium-chitosan nanocomposite (CS- SeNPs). Previous studies have demonstrated the antioxidant properties of CS-SeNPs to be more efficient as 87.45 ± 7.63 % (in ABTS) (Zhai et al., 2017), 20.2 ± 0.6 % (in DPPH) (Bai et al., 2020), 83.71 % (in ABTS) (Chen et al., 2015)), and 60± 2.5 % (in DPPH) (Khiralla et al., 2020). Moreover, the metal ion chelators were accepted as promising agents for treating AD as it is one of the metal ions' dysmetabolisms. Thus, Se itself can act as a viable therapeutic target to alleviate AD. As beta-amyloid peptide aggregates remain a major offender in the occurrence of AD, Chitosan itself can act in the dissolution of insoluble and preformed soluble aggregates. They act by retracting the formation of the secondary structure (beta sheet) of amyloid protein by stabilizing the alpha-helical structure, preventing aggregate formation, which is because of the effect of pH, which makes the peptide have a net negative charge of -3 and Chitosan to have a positive charge, resulting in the formation of ionic or hydrogen bonds. The effect of CS-SeNPs on cell lines (SH-SY-5Y) was studied in previous reports by Jha et al. (2019). They reported that the polymeric nanoparticles alone tend to disintegrate the amyloid plaques formed in the brain.

Chitosan scaffolds assist in anchoring and promoting osteoblast cell growth and in the production of mineralized bone matrix. Hydrogels made of Chitosan stand out for promoting cartilaginous tissue regeneration and effectively promoting chondrogenic activity. The potential of

Table 3
Chitosan – Available sources and its extraction methods.

S. No	Organism	Source	Pre-treatment	Demineralization	Deproteination	Decolouration	Post treatment	Deacetylation \ Chitosan isolation	Purification	Refs.
1.	Cray Fish	Shell	The shells were washed and cut into small pieces.	The sample was demineralized in RT in the 1 M HCl.	After demineralization the samples were treated with 1 M NaOH at 105–110 °C. This treatment will be carried for several times.			The obtained chitin was treated with strong NaOH at normal atmosphere. Then it was heated in the autoclave under two atmosphere pressure for 10–15 h.		Abdou et al. (2008)
2.	Shrimp (*M. monoceros*)	Shell	The shells were washed and dried.	Followed by the deproteination the samples were treated with 1.5 M HCl in the ratio of (1:10; w/v) at 25 °C for 6 h.	The shells were added in water (1:2; w/v) then grounded and boiled at 90 °C for 20 min. Then pH was adjusted to 8. The crude *B. cereus* SV1 protease enzyme was added and incubated at 40 °C for 3 h to digest the proteins. The enzyme activity was stopped by heating the samples up to 90 °C for 20 min. Then centrifugation was done at 5000 g for 20 min to separate insoluble and soluble fractions. The solid phase was washed and dried at 60 °C for 1hr.		The obtained chitin was filtered using 4 layers of gauze with the help of Vacuum pump and finally washed with deionized water to neutralize and kept for freeze dry.	The chitin was treated with 50 % NaOH for 4 h at 80 °C to obtain chitosan. The chitosan was washed and dried at 50 °C for overnight.		Manni et al. (2010)
3.	Fungi, *(Aspergillus niger, sRhizopus oryzae, Lentinus edodes and Pleurotus sajo-caju,)*		The fungus was recovered using (no.1, Whatman) filter and Yeast cells were harvested by centrifugation (8000 g: 30 min). Finally obtained products were washed in distilled water and dried at 65 °C.				The dried fungal and yeast cells were grounded and mixed in the 1 M NaOH solution (1:30 w/v) and autoclaved for 15 min. The insoluble materials were collected by centrifugation for 15 min at 12,000 g. Then it was washed and recentrifuged at neutral pH. The residue was extracted using 2 % acetic acid (1:40; w/v) for 15 min at 12,000 g.	The pH of the supernatant was altered to 10 using 2 m NaOH and centrifuged for 15 min at 12,000 g. The sedimented chitosan was washed with distilled water, 95 % ethanol and acetone and dried at 60 °C.		Pochanavanich and Suntornsuk (2002)
4.	Pink shrimp (*Farfantepenaeus brasiliensis*)	Shell						66 g of chitin was added in 4 L of concentrated NaOH and agitated for 50 rpm at 130±1 °C.	The obtained chitosan was mixed with 1 % Acetic acid. Then the sample was centrifuged at 6650 g for 30 min to remove	Moura et al. (2011)

(*continued on next page*)

Table 3 (*continued*)

S. No	Organism	Source	Pre-treatment	Demineralization	Deproteination	Decolouration	Post treatment	Deacetylation \ Chitosan isolation	Purification	Refs.
									insoluble particles. The supernatant was added with NaOH and neutralized at the pH 7.0. The purified chitosan was obtained as supernatant after centrifugation.	
5.	Shrimp (Crangon crangon)	Shell	The shells were washed in the tap water and stored in −20 °C. The shells were thawed at room temperature under laminar flow.	The thawed shells were placed in the stirrer with 10 %HCL for 20 min. Then the shells were washed with tap water and rinsed in deionised water.	The demineralized shells were suspended in the 2 N NaOH (1:10) and kept in the shaker at 100 rpm for 6 h at 37 °C. Then the NaOH and HCl was removed and kept in the thermostat water bath for 2–5 h at 30–65 °C.		Further the chitin was washed and dried overnight at 100±5 °C.	1 g of the chitin samples were added in the 20 ml of 50 % NaOH solution and kept at 30–65 °C for 2–5 h. Air atmosphere in the bottle was exchanged against 2 bar nitrogen at 105 °C for 1–4 h. The bottle was depressurised and cooled in laminar flow hood. The NaOH was removed, washed and dried.		Bajaj et al. (2011)
6.	*Crustaceans (*L. *antarcticus, P. granulosa, P. vulgaris)*	Chitin						The chitin was treated with 50 % NaOH at 110 °C for 4 h under N2 atmosphere in the ratio of 10 ml/g. The N-Deacetylated chitosan were treated with 0.1 M HCl for 12 h in the stirring conditions. Then it was filtered through 5 μm TMTP membrane. Then 1.5 ml (31.36 mM KNO2) added and stirred for 120 min at 35 °C. The decartelization is stopped by adding Acetone.		Galed et al. (2005)
7.	Jumbo squid (*Dosidicus gigas*)	β-Chitin Pens						1. The β-Chitin was treated with 40–50 % NaOH in 60–90 °C for 2–6 h for three cycles in the ration of (1:20). 2. (50 % w/w) KOH was dissolved in the 95 % EtOH (25 % w/w) and non-ethylene glycol (25 % w/w). The β-Chitin was		Jung and Zhao (2011)

(*continued on next page*)

Table 3 (*continued*)

S. No	Organism	Source	Pre-treatment	Demineralization	Deproteination	Decolouration	Post treatment	Deacetylation \ Chitosan isolation	Purification	Refs.
								added in KOH solution in the ration of (1:20) and kept in 90–120 °C for 2–6 h for three cycles.		
8.	Prawn (Litopenaeus vannamei)	Shell	The flesh was removed by washing the shells with (60 °C) hot water. Then it was dried, powdered and sieved using the 60–120 μm mesh.	The deproteinized powder was treated in 1 % HCl solution in the ration (w/v 1:10) at 25 °C for 24 h.	The powdered shell was treated with 5 % NaOH solution (W/V 1:8) and refluxed at 60 °C for 2 h. Then dried at 60 °C at Vacuum Oven.	The pigments in the chitin were removed by treating with the acetone at RT (Room Temperature) for 24 h.	The obtained chitin was washed in distilled water and dried at 50 °C in vacuum oven	The isolated chitin was treated with the 25–50 % of NaOH at 80–100 °C for 5–10 h.	–	Mohammed et al. (2013)
9.	Desert locust (*Schistocerca gregaria*)	Exoskeletons	In the Exoskeleton the tissues were removed, washed, dried, grounded and sieved using 250 μm mesh.	1 g of grounded exoskeleton was taken in the 15 ml of 1 M HCl solution and kept in the ambient temperature.	1 M NaOH was added and kept in the 100 °C for 8 h. (Alkaline treatment)		After alkaline treatment chitin was washed in distilled water and dried at 50 °C in vacuum oven.	The isolated Chitin was treated with 50 % NaOH(15 ml/g) at 100 °C for 8 h. The obtained Chitosan was washed in distilled water and dried at 50 °C for 24 h in vacuum oven.	The obtained Chitosan was dissolved in 2 % Acetic acid and reprecipitated in 20 % NaOH solution. The precipitate was washed and dried.	Marei et al. (2016)
10.	Beetles (*Calosoma rugosa*)	Exoskeletons	In Exoskeleton the tissues were removed, washed, dried, grounded and sieved using 250 μm mesh.	The 1 g of grounded exoskeleton was taken in the 15 ml of 1 M HCl solution and kept in the ambient temperature.	1 M NaOH was added and kept in 100 °C for 8 h. (Alkaline treatment)		After alkaline treatment chitin was washed in distilled water and dried at 50 °C in vacuum oven	The isolated Chitin was treated with 50 % NaOH(15 ml/g) at 100 °C for 8 h. The obtained Chitosan was washed in distilled water and dried at 50 °C for 24 h in vacuum oven.	The obtained Chitosan was dissolved in 2 % Acetic acid and reprecipitated in 20 % NaOH solution. The precipitate was washed and dried.	Marei et al. (2016)
11.	Honey bees (*Apis mellifera*)	Exoskeletons	In Exoskeleton the tissues were removed, washed, dried, grounded and sieved using 250 μm mesh.	The 1 g of grounded exoskeleton was taken in the 15 ml of 1 M HCl solution and kept in the ambient temperature.	1 M NaOH was added and kept in 100 °C for 8 h. (Alkaline treatment)		After alkaline treatment chitin was washed in distilled water and dried at 50 °C in vacuum oven	The isolated Chitin was treated with 50 % NaOH(15 ml/g) at 100 °C for 8 h. The obtained Chitosan was washed in distilled water and dried at 50 °C for 24 h in vacuum oven.	The obtained Chitosan was dissolved in 2 % Acetic acid and reprecipitated in 20 % NaOH solution. The precipitate was washed and dried.	Marei et al. (2016)
12.	Shrimp (*Peanous mondon*)	Shells	In the shell the tissues were removed, washed, dried, grounded and sieved using 250 μm mesh.	The 1 g of grounded shell was taken in the 15 ml of 1 M HCl solution and kept in the ambient temperature.	1 M NaOH was added and kept in the 100 °C for 8 h. (Alkaline treatment)		After alkaline treatment chitin was washed in distilled water and dried at 50 °C in vacuum oven	The isolated Chitin was treated with 50 % NaOH(15 ml/g) at 100 °C for 8 h. The obtained Chitosan was washed in distilled water and dried at 50 °C for 24 h in vacuum oven.	The obtained Chitosan was dissolved in 2 % Acetic acid and reprecipitated in 20 % NaOH solution. The precipitate was washed and dried.	Marei et al. (2016)

Chitosan for nerve regeneration has been established *In vitro* and *in vivo*. Chitosan-based materials also promote neurons' adhesion, survival, and neurite outgrowths (Victor et al., 2020). Fig. 3 depicts the use of Chitosan as an effective drug delivery system for NDDs.

10. Chitosan – drug delivery and derivatives for NDD

Concerns about the blood-brain barrier (BBB) and blood-spinal cord barrier, in particular neurodegenerative diseases (NDD), continue to be the main issues in neurological illnesses. The blood-brain barrier (BBB), out of all these biological barriers, is the one that makes it most difficult for medications to enter the brain (Akhtar et al., 2021). Delivery of brain-targeted nanoparticles with desired properties and adaptable qualities is made possible by the feasibility of surface modification of the chitosan structure. To improve BBB penetration, cell compatibility, and serum stability, modified Chitosan is also effective in capping the surfaces of other nanocarrier materials such as PLGA (poly (lactic-co-glycolic acid)) and PLA (poly lactic acid) (Wang et al., 2010). By using a promising nanoparticle, the medicine would be able to pass the blood-brain barrier (BBB) more readily and avoid cytotoxicity to a greater extent (Baysal et al., 2017; Sánchez-López et al., 2018). Focus has also switched to chitosan-collagen nanocomposites since their scaffolds have demonstrated outstanding potential in developing protein-polysaccharide drug delivery vehicles (Rezaii et al., 2019; Zeissler et al., 2016). By forming polyplexes, the chitosan derivative's hydrophobic component helps release the anionic ions bound to the Chitosan. The simple, less toxic, biocompatible, more stable, and completely biodegradable nature of chitosan nanoparticles has employed them for various therapeutic purposes. Blood stability, BBB epithelial surface adhesion, and blood compatibility are necessary to treat neurodegenerative diseases (Szebeni, 2012).

Chitosan has varied kinds of derivatives, which would be very beneficial for drug delivery among NDDs. Various techniques can be used to create drug-loaded chitosan nanoparticles depending on the structural properties of the Chitosan and the makeup of the drug. The N-trimethyl chitosan (TMC) is a type of Chitosan that has received extensive research for brain targeting with anti-AD because positive charged TMC and anionic sialic acid residues of glycoprotein present on the BBB undergo electrostatic interactions (Sarvaiya & Agrawal, 2015). It has been discussed how TMC can target the brain by altering the surface of PLGA nanoparticles. The delivery of Co-enzyme Q10 and 6-coumarin by TMC/PLGA-NP for the treatment of AD-related neurodegeneration was confirmed by senile plaque and biochemical testing to have effects that are specifically targeted to the brain (Wang et al., 2010). Other derivatives of Chitosan are the use of tween 80 coated chitosan, PEGylated Chitosan, and zwitter ionic chitosan derivatives (Wilson et al., 2010), which is another standard method for influencing BBB permeability of neuroprotective drugs. In contrast, it was discovered that the amount of medication transported by Tween 80 coated chitosan nanoparticles across the BBB was equal to that of unmodified chitosan nanoparticles (Bhavna et al., 2014) (Fig. 4).

DNA-loaded chitosan particles are more durable when stored, so using Chitosan as a vector for gene therapy is essential (Duceppe & Tabrizian, 2010). Using Chitosan as a protein carrier can assist in extending the biological activity of protein therapeutics *in vivo* by protecting them from enzyme degradation and regulating drug release to meet the goal of sustained or controlled release (Lü et al., 2010). Chitosan shields the DNA from nuclease degradation by combining with the negatively charged DNA to form a polyelectrolyte complex. The effectiveness of transfection is increased by this protection (Agnihotri et al., 2004). It is possible to transmit genes with and without the aid of viruses. A naturally occurring cationic polysaccharide with an excellent affinity for DNA is Chitosan (Renugalakshmi et al., 2011). Increase Chitosan's ability to transport DNA and its solubility; the quaternary ammonium group was modified to create quaternary Chitosan (Li et al., 2015). Derivatization of Chitosan can increase its stability and targeting potential; for instance, Hu et al. (2015) used a chitosan-based glycolipid-like nanocarrier to deliver siRNA with a redox response to specific targets. As Chitosan and its derivatives are studied more in-depth, the evidence is mounting that the organic mixture of chitosan bioactivities and pharmaceuticals will enhance the progress of drug preparations and be extensively used in novel drug dosage forms. The development of chitosan vehicles that can control the release of medication, particularly for NDDs, is one of the research fields that will be studied in the future.

11. Challenges to use Chitosan as drug deliverables for NDD

One significant area for improvement is establishing a long enough shelf life for chitosan formulations because unstable chitosan-based systems limit their practical application. Controlling environmental parameters, adjusting production settings (such as temperature), adding the right stabilizing component, creating chitosan blends with other polymers, or altering the structure of the Chitosan using chemical or ionic agents can all improve stability (Szymańska & Winnicka, 2015). The molecular mass, polydispersity, deacetylation level, purity threshold, and amount of moisture are all important factors that affect how quickly and how Chitosan can get degraded. Chitosan can get easily degraded both *in-vivo* and *in-vitro* mode. Lysozyme, a general protease found in all mammalian tissues, is primarily responsible for breaking down Chitosan *in vivo*. This process results in nontoxic oligosaccharides that can either be expelled or added to glycosaminoglycans and glycoproteins (Kurita et al., 2000). Low-molecular Chitosan is often prepared

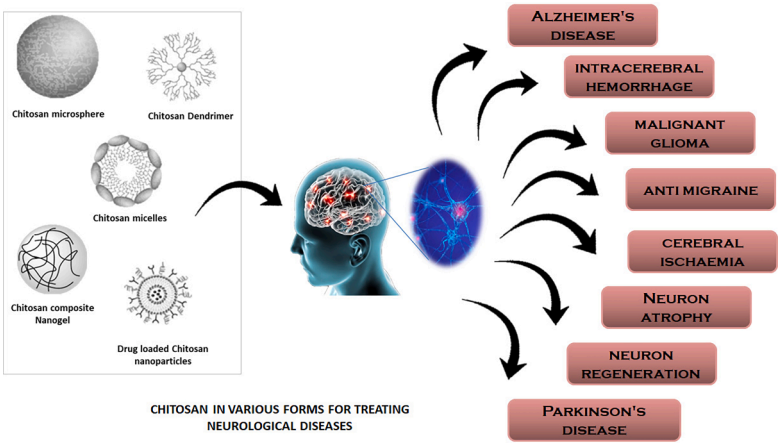

Fig. 3. Chitosan forms for various Neurodegenerative diseases: Chitosan can be used in various forms for the treatment of a number of neurodegenerative diseases and it includes chitosan microsphere, dendrimer, micelles, nanogel and nanoparticles in diseases such as AD, PD, Migraine etc.

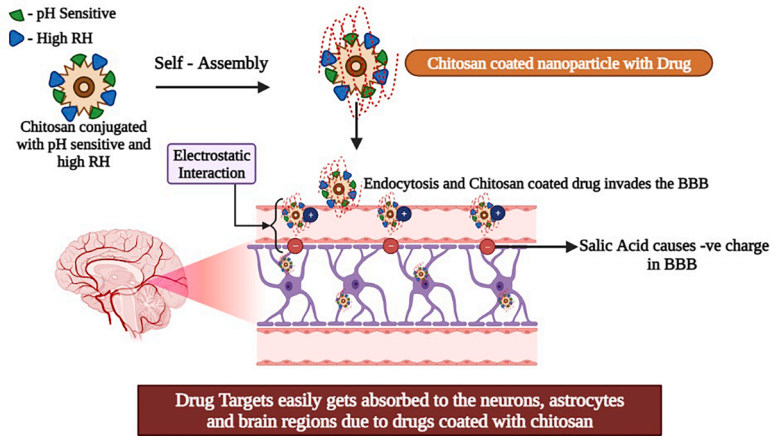

Fig. 4. Chitosan as drug delivery for Neurodegenerative diseases: Drugs conjugated with chitosan makes it easy to delivery the drugs for neurodegenerative diseases. The release of chitosan coated drugs easily diffusions the drugs to astrocytes and neurons due to the positive and negative charges.

Table 4
Explanation of studies using Chitosan as drug delivery for overall neurological diseases.

S. No	Pharmaceutical form of Chitosan and its derivatives used	Source of Therapeutic drug	*In vitro/ In vivo* model	Dosage	Pharmaceutical applications	Refs.
1.	Brain-derived neurotrophic factor (BDNF) loaded chitosan microspheres	Commercially purchased	PC-12 cells	1 mg/mL	Detection of neural differentiation and axonal promoting activity of BDNF in PC-12 cells	Aranaz et al. (2023)
2.	Piracetam-loaded magnetic chitosan nanoparticles	Commercially purchased	Female Albino rats	200 mg/kg	Mitigates Thiacloprid induced brain toxicity	Abomosallam et al. (2023)
3.	Nirurifiavone-loaded chitosan nanoparticles	*Phyllanthus niruri*	SH-SY-5Y, Wistar rats	250 μg/mL, 0.125 mg/kg	Targets blood–brain barrier and also in treating Alzheimers Disease	Rajamanickam and Manju (2023)
4.	Resveratrol loaded chitosan nanoparticles	Commercially purchased	Mice		Alleviates glucolipid metabolism disorder-associated cognitive impairment in Alzheimer's disease	Yang et al. (2023)
5.	L-arginine loaded chitosan nanoparticles	Commercially purchased	Wistar rat	500 mg/kg	Ameliorates aging-induced neuron atrophy and autophagy	Zargani et al. (2023)
6.	Transferrin-decorated chitosan nanoparticles	Commercially purchased	RPMI 2650 and U87 glioblastoma cells	5mg	Enhances delivery of protein through nose-to-brain	Gabold et al. (2023)
7.	Chitosan-g-poly (N-isopropylacrylamide)	Synthesized compound	Female New Zealand white rabbits		Enhances myelin growth and neuron regeneration in glaucoma related neurodegeneration	Luo et al. (2020)
8.	Cannabidiol Coated by Nano-Chitosan	Commercially purchased	Male Wistar rat	200 mg/kg	Enhances cannabinoid receptor type 1 and 2 which results in increased learning and memory in Alzheimers induced rat	Amini and Abdolmaleki (2022)
9.	Chitosan-Mangafodipir nanoparticles for intranasal delivery of siRNA and DNA	Commercially purchased	NIH3T3 cells/ transgenic green mice	20 μM	For treating neurodegenerative disease by delivery of siRNA and dsDNA (liberating payload from nose to brain; to develop disease-modifying therapeutics)	Sanchez-Ramos et al. (2018)
10.	Chitosan nanoparticles and HAMC composites	Commercially purchased	Rats	10 mg/kg	For treatment of Intracerebral hemorrhage through intranasal drug delivery	Guo et al. (2019)
11.	Rutin-encapsulated chitosan nanoparticles	Commercially purchased	Wistar rats	1:1	For treatment of Cerebral Ischemia	Ahmad et al. (2016)
12.	Chitosan glucamate microcarrier	Commercially purchased	Wistar rats	5 mg/ml	For treatment of anti-migraine	Gavini et al. (2013)
13.	Ellagic acid loaded chitosan/ β-glycerophosphate (Ch/β-GP) thermo-sensitive gel	Commercially purchased	U87 and C6 glioma cells	660mM	For treatment of Brain cancer	Kim et al. (2010)
14.	Curcuminoid loaded Hyaluronic acid/chitosan nanoparticles	Commercially purchased	C6 cells	2 mg/mL	For treating Malignant glioma	Yang et al. (2015)
15.	Lactoferrin-coated chitosan hydrochloride/hyaluronic acid/ PEG nanoparticles	Commercially purchased	BCECs and C6 cells/ ICR mice	5 μg/mL/ 1.25 mg/kg	For treating Malignant glioma through targeting Blood Brain Barrier	Xu et al. (2017)
16.	Tacrine-loaded chitosan nanoparticles	Commercially purchased	Albino Wistar rat	1:1	Pre-clinical assessment for treating Alzheimer's disease	Wilson et al. (2010)
17.	Glycol chitosan and dextran sulfate nanoparticles	Commercially purchased	*In vitro*		For the treatment of Brain cancer	Saboktakin et al. (2011)
18.	TAT peptide-tagged PEGylated chitosan nanoparticles	Chemically synthesized	Mouse neuroblastoma cells (Neuro 2a)	40 μM SiRNA	For treating Neurodegenerative disease by targeting Ataxin-1 gene	Malhotra et al. (2013)

under controlled circumstances by *In vitro* degradations of Chitosan through oxidation, chemical, or enzymatic hydrolysis reactions (Ma et al., 2014). Irrespective of the method of deterioration of Chitosan, the process often starts with the N-acetyl linkage, which means deacetylation and random splitting of -1,4-glycosidic, which links depolymerization.

The results are an increase in deacetylation degree and a decrease in average molecular weight. Additionally, the depolymerization of Chitosan may produce free radicals, which trigger oxidation processes (Mucha & Pawlak, 2022). As a result, chitosan material should be highly pure and free of impurities, including endotoxins, when applicable (Li et al., 2018). Chitosan has much potential for tissue engineering and drug delivery systems; however, scaling up these applications for pharmaceutical use is difficult due to its low long-term stability. During storage, chitosan experiences slow chain degradation, followed by the elimination of its functional groups, which causes the irreversible loss of its physicochemical properties, which might be because Chitosan has significant hygroscopic qualities and because chitosan materials from different sources have very different molecular weights, molecular weight distributions, levels of deacetylation, and purity. Due to Chitosan's high susceptibility to outside factors, its structure may be stressed and deteriorate due to processing conditions (such as heating or freezing). Consequently, even though chitosan-based services have been the subject of broad investigation in the biomedical field, manufacturing Chitosan as a pharmaceutical ingredient for NDDs still needs to overcome a few obstacles (Table 4).

12. Future directions and recommendations for the use of Chitosan in NDD therapies

Since there are no general guidelines for maintaining chitosan-based goods during storage, pre-formulation research and choosing the best storage conditions are crucial to ensuring the maximum stability of Chitosan for drug delivery. The following is an explanation of some recommendations for future studies using Chitosan for medication delivery:

- In addition to its physiological properties like immunology or biological breakdown, Chitosan's purity level greatly impacts a substance's solubility and stability.
- It must be noted that heat generation during capsule manufacturing is caused by the compression force, which could impact the dispersion of the chitosan molecular weight and prevent deacetylation.
- The physicochemical and mechanical properties of chitosan-based systems may alter due to variations in the moisture content of the chitosan material during storage.
- The rate of drug discharge outline of the chitosan matrix can be altered by storing it at high relative humidity and modifying its water-uptake capacity.
- To avoid the loss of moisture and hardness and improve the mechanical tablet strength, the exposure temperature should be kept below 40 °C.
- Filter sterilization could eliminate microbial impurities and ensure that heat-labile liquid chitosan formulations are pure.
- The mechanical and water-uptake properties of chitosan formulations will be influenced by adding stabilizing chemicals to chitosan films .

13. Conclusion

Chitosan is a promising novel excipient for pharmaceutical preparations since it is a biodegradable polymer with good characteristics. Chitosan nanoparticles help deliver medicines and boost their therapeutic potency. They can be employed in oral drug delivery because they loosen the mucosal membrane's tight junctions, which improves absorption. They make a variety of medications more nasally absorbable by increasing their permeability. They aid in the mucosal drug delivery process by enhancing the absorption of hydrophilic compounds. They serve as an adjuvant in the administration of vaccines. The physiochemical characteristics of chitosan NPs are primarily responsible for these uses. These include *in-situ* gelling ability, mucoadhesiveness, absorption-enhancing capacity, biocompatibility, and biodegradability. In conclusion, conducting more extensive recharge on Chitosan and its derivatives for NDDs would help us develop novel dosage forms of drugs.

Funding

No funding was obtained to conduct this review article.

CRediT authorship contribution statement

Mahalaxmi Iyer: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Ajay Elangovan:** Writing – original draft, Data curation. **Ramya Sennimalai:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Harysh Winster Suresh Babu:** Writing – original draft, Data curation. **Saranya Thiruvenkataswamy:** Writing – original draft, Data curation. **Jayalakshmi Krishnan:** Writing – review & editing. **Mukesh Kumar Yadav:** Writing – review & editing. **Abilash Valsala Gopalakrishnan:** Writing – review & editing. **Arul Narayanasamy:** Writing – review & editing. **Balachandar Vellingiri:** Writing – review & editing, Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgments

We thank Central University of Punjab, Bathinda, Bharathiar University, Coimbatore, and other universities for providing the facilities to conduct this review article.

References

Abdou, E. S., Nagy, K. S. A., & Elsabee, M. Z. (2008). Extraction and characterization of Chitin and Chitosan from local sources. *Bioresource Technology, 99*(5), 1359–1367. https://doi.org/10.1016/j.biortech.2007.01.051

Abomosallam, M., Hendam, B. M., Abdallah, A. A., Refaat, R., Elshatory, A., & Gad El Hak, H. N. (2023). Neuroprotective effect of piracetam-loaded magnetic chitosan nanoparticles against thiacloprid-induced neurotoxicity in albino rats. *Inflammopharmacology, 1–23*. https://doi.org/10.1007/s10787-023-01151-x

Agnihotri, S. A., Mallikarjuna, N. N., & Aminabhavi, T. M. (2004). Recent advances on chitosan-based micro- and nanoparticles in drug delivery. *Journal of Controlled Release, 100*(1), 5–28. https://doi.org/10.1016/j.jconrel.2004.08.010

Ahmad, N., Ahmad, R., Naqvi, A. A., Alam, M. A., Ashafaq, M., Samim, M., … Ahmad, F. J. (2016). Rutin-encapsulated chitosan nanoparticles targeted to the brain in the treatment of Cerebral Ischemia. *International Journal of Biological Macromolecules, 91*, 640–655. https://doi.org/10.1016/j.ijbiomac.2016.06.001

Akhtar, A., Andleeb, A., Waris, T. S., Bazzar, M., Moradi, A. R., & Awan, N. R. (2021). Neurodegenerative diseases and effective drug delivery: A review of challenges and novel therapeutics. *Journal of Controlled Release, 330*, 1152–1167. https://doi.org/10.1016/j.jconrel.2020.11.021

Alhodieb, F. S., Barkat, Md. A., Barkat, H. A., Hadi, H. A., Khan, M. I., Ashfaq, F., et al. (2022). Chitosan-modified nanocarriers as carriers for anticancer drug delivery: Promises and hurdles. *International Journal of Biological Macromolecules, 217*, 457–469. https://doi.org/10.1016/j.ijbiomac.2022.06.201

Amini, M., & Abdolmaleki, Z. (2022). The effect of cannabidiol coated by nano-chitosan on learning and memory, hippocampal CB1 and CB2 levels, and amyloid plaques in an Alzheimer's disease rat model. *Neuropsychobiology, 81*, 171–183. https://doi.org/10.1159/000519534Amini

Anitha, A., Sowmya, S., Kumar, P. T. S., Deepthi, S., Chennazhi, K. P., Ehrlich, H., et al. (2014). Chitin and Chitosan in selected biomedical applications. *Progress in Polymer Science, 39*(9), 1644–1667. https://doi.org/10.1016/j.progpolymsci.2014.02.008

Aranaz, I., Acosta, N., Revuelta, J., Bastida, A., Gómez-Casado, V., Civera, C., et al. (2023). Fast and sustained axonal growth by BDNF released from Chitosan microspheres. *Marine Drugs, 21*(2), 91. https://doi.org/10.3390/md21020091

Aranaz, I., Alcántara, A. R., Civera, M. C., Arias, C., Elorza, B., & Caballero, A. H. (2021). Chitosan: An overview of its properties and applications. *Polymers, 13*(19). https://doi.org/10.3390/polym13193256. Multidisciplinary Digital Publishing Institute (MDPI).

Azeem, M., Batool, F., Iqbal, N., & Ikram-ul-Haq. (2017). Chapter 1—Algal-based biopolymers. K. M . Zia, M. Zuber, & M. Ali (Eds.). *Algae based polymers, blends, and composites* (pp. 1–31). Elsevier. https://doi.org/10.1016/B978-0-12-812360-7.00001-X.

Bai, S., Wang, L., Ma, F., Zhu, S., Xiao, T., Yu, T., et al. (2020). Self-assembly biochar colloids mycelial pellet for heavy metal removal from aqueous solution. *Chemosphere, 242*, Article 125182. https://doi.org/10.1016/j.chemosphere.2019.125182

Bajaj, M., Winter, J., & Gallert, C. (2011). Effect of deproteination and deacetylation conditions on viscosity of Chitin and Chitosan extracted from Crangon crangon shrimp waste. *Biochemical Engineering Journal, 56*(1), 51–62. https://doi.org/10.1016/j.bej.2011.05.006

Balachandar, V., Kumar, R. M., Arun, M., Devi, S. M., Sasikala, K., & Kumar, S. S. (2012). Huntington's Disease-A neurodegenerative disorder characterized by CAG repeats in IT15 gene. *Journal of Medical Genetics, 49*, S68. –S68.

Barchet, T. M., & Amiji, M. M. (2009). Challenges and opportunities in CNS delivery of therapeutics for neurodegenerative diseases. *Expert Opinion on Drug Delivery, 6*(3), 211–225. https://doi.org/10.1517/17425240902758188

Barclay, T. G., Day, C. M., Petrovsky, N., & Garg, S. (2019). Review of polysaccharide particle-based functional drug delivery. *Carbohydrate Polymers, 221*, 94–112. https://doi.org/10.1016/j.carbpol.2019.05.067

Bastiaens, L., Soetemans, L., D'Hondt, E., & Elst, K. (2019). Sources of Chitin and Chitosan and their Isolation. *Chitin and chitosan* (pp. 1–34). John Wiley & Sons, Ltd. https://doi.org/10.1002/9781119450467.ch1

Baysal, I., Ucar, G., Gultekinoglu, M., Ulubayram, K., & Yabanoglu-Ciftci, S. (2017). Donepezil loaded PLGA-b-PEG nanoparticles: Their ability to induce destabilization of amyloid fibrils and to cross blood brain barrier *in vitro*. *Journal of Neural Transmission, 124*(1), 33–45. https://doi.org/10.1007/s00702-016-1527-4

Beaney, P., Lizardi-Mendoza, J., & Healy, M. (2005). Comparison of chitins produced by chemical and bioprocessing methods. *Journal of Chemical Technology & Biotechnology, 80*(2), 145–150. https://doi.org/10.1002/jctb.1164

Bellich, B., D'Agostino, I., Semeraro, S., Gamini, A., & Cesàro, A. (2016). The good, the bad and the ugly" of Chitosans. *Marine Drugs, 14*(5), Article 5. https://doi.org/10.3390/md14050099

Bhavna, Md, S., Ali, M., Baboota, S., Sahni, J. K., Bhatnagar, A., et al. (2014). Preparation, characterization, *in vivo* biodistribution and pharmacokinetic studies of donepezil-loaded PLGA nanoparticles for brain targeting. *Drug Development and Industrial Pharmacy, 40*(2), 278–287. https://doi.org/10.3109/03639045.2012.758130

Bo, M., Bavestrello, G., Kurek, D., Paasch, S., Brunner, E., Born, R., et al. (2012). Isolation and identification of Chitin in the black coral Parantipathes larix (Anthozoa: Cnidaria). *International Journal of Biological Macromolecules, 51*(1), 129–137. https://doi.org/10.1016/j.ijbiomac.2012.04.016

Byun, H. G., Kim, Y. T., Park, P. J., Lin, X., & Kim, S. K. (2005). Chitooligosaccharides as a novel β-secretase inhibitor. *Carbohydrate Polymers, 61*(2), 198–202. https://doi.org/10.1016/j.carbpol.2005.05.003

Calvo, P., Vila-Jato, J. L., & Alonso, M. J. (1997). Evaluation of cationic polymer-coated nanocapsules as ocular drug carriers. *International Journal of Pharmaceutics, 153*(1), 41–50. https://doi.org/10.1016/S0378-5173(97)00083-5

Chen, W., Li, Y., Yang, S., Yue, L., Jiang, Q., & Xia, W. (2015). Synthesis and antioxidant properties of Chitosan and carboxymethyl chitosan-stabilized selenium nanoparticles. *Carbohydrate Polymers, 132*, 574–581. https://doi.org/10.1016/j.carbpol.2015.06.064

Chowdhury, A., Kunjiappan, S., Panneerselvam, T., Somasundaram, B., & Bhattacharjee, C. (2017). Nanotechnology and nanocarrier-based approaches on treatment of degenerative diseases. *International Nano Letters, 7*(2), 91–122. https://doi.org/10.1007/s40089-017-0208-0

Dai, X., Chang, P., Zhu, Q., Liu, W., Sun, Y., Zhu, S., et al. (2013). Chitosan oligosaccharides protect rat primary hippocampal neurons from oligomeric β-amyloid 1-42-induced neurotoxicity. *Neuroscience Letters, 554*, 64–69. https://doi.org/10.1016/j.neulet.2013.08.046

de Oliveira Pedro, R., Goycoolea, F. M., Pereira, S., Schmitt, C. C., & Neumann, M. G. (2018). Synergistic effect of quercetin and pH-responsive DEAE-chitosan carriers as drug delivery system for breast cancer treatment. *International Journal of Biological Macromolecules, 106*, 579–586. https://doi.org/10.1016/j.ijbiomac.2017.08.056

Dhanavel, S., Nivethaa, E. A. K., Narayanan, V., & Stephen, A. (2017). *In vitro* cytotoxicity study of dual drug loaded chitosan/palladium nanocomposite towards HT-29 cancer cells. *Materials Science and Engineering: C, 75*, 1399–1410. https://doi.org/10.1016/j.msec.2017.03.058

Dhingra, A. K., Rathi, V., & Chopra, B. (2021). Chapter 3.1.1—Resveratrol. T. Belwal, S. M . Nabavi, S. F . Nabavi, A. R . Dehpour, & S. Shirooie (Eds.). *Naturally occurring chemicals against Alzheimer's disease* (pp. 33–47). Academic Press. https://doi.org/10.1016/B978-0-12-819212-2.00037-2.

Dhivya, V., & Balachandar, V. (2017). Cell replacement therapy is the remedial solution for treating Parkinson's disease. *Stem Cell Investigation, 4*. https://doi.org/10.21037/sci.2017.06.08

Dodane, V., & Vilivalam, V. D. (1998). Pharmaceutical applications of Chitosan. *Pharmaceutical Science & Technology Today, 1*(6), 246–253. https://doi.org/10.1016/S1461-5347(98)00059-5

Dong, X. (2018). Current Strategies for Brain Drug Delivery. *Theranostics, 8*(6), 1481–1493. https://doi.org/10.7150/thno.21254

Duceppe, N., & Tabrizian, M. (2010). Advances in using chitosan-based nanoparticles for *in vitro* and *in vivo* drug and gene delivery. *Expert Opinion on Drug Delivery, 7*(10), 1191–1207. https://doi.org/10.1517/17425247.2010.514604

Eftekharzadeh, B., Khodagholi, F., Abdi, A., & Maghsoudi, N. (2010). Alginate protects NT2 neurons against H2O2-induced neurotoxicity. *Carbohydrate Polymers, 79*(4), 1063–1072. https://doi.org/10.1016/j.carbpol.2009.10.040

Ehrlich, H., Ilan, M., Maldonado, M., Muricy, G., Bavestrello, G., Kljajic, Z., et al. (2010). Three-dimensional chitin-based scaffolds from Verongida sponges (Demospongiae: Porifera). Part I. Isolation and identification of Chitin. *International Journal of Biological Macromolecules, 47*(2), 132–140. https://doi.org/10.1016/j.ijbiomac.2010.05.007

Elangovan, A., Babu, H. W. S., Iyer, M., Gopalakrishnan, A. V., & Vellingiri, B. (2023a). Untangle the mystery behind DS-associated AD – Is APP the main protagonist? *Ageing Research Reviews, 87*, Article 101930. https://doi.org/10.1016/j.arr.2023.101930

Elangovan, A., Venkatesan, D., Selvaraj, P., Pasha, Md. Y., Babu, H. W. S., Iyer, M., et al. (2023b). miRNA in Parkinson's disease: From pathogenesis to theranostic approaches. *Journal of Cellular Physiology, 238*(2), 329–354. https://doi.org/10.1002/jcp.30932

Esko, J. D., Bertozzi, C., & Schnaar, R. L. (2015). Chemical tools for inhibiting glycosylation. A. Varki, R. D . Cummings, J. D . Esko, P. Stanley, G. W . Hart, M. Aebi, A. G . Darvill, T. Kinoshita, N. H . Packer, J. , et al. (Eds.). *Essentials of glycobiology* (3rd ed.). Cold Spring Harbor Laboratory Press http://www.ncbi.nlm.nih.gov/books/NBK453074/.

Fenn, J. P., Shanwaz, D., Keshavarao, S., & Vellingiri, B. (2016). Cytogenetic study and compared with measurements of oxidative stress and PINK1 gene in Parkinson Disease (PD) patients. *Parkinsonism & Related Disorders, 22*, e168. https://doi.org/10.1016/j.parkreldis.2015.10.408

Fogel, D. B. (2018). Factors associated with clinical trials that fail and opportunities for improving the likelihood of success: A review. *Contemporary Clinical Trials Communications, 11*, 156–164. https://doi.org/10.1016/j.conctc.2018.08.001

Gabold, B., Adams, F., Brameyer, S., Jung, K., Ried, C. L., Merdan, T., & Merkel, O. M. (2023). Transferrin-modified chitosan nanoparticles for targeted nose-to-brain delivery of proteins. *Drug Delivery and Translational Research, 13*, 822–838. https://doi.org/10.1007/s13346-022-01245-z

Galed, G., Miralles, B., Paños, I., Santiago, A., & Heras, Á. (2005). N-Deacetylation and depolymerization reactions of chitin/chitosan: Influence of the source of chitin. *Carbohydrate Polymers, 62*, 316–320. https://doi.org/10.1016/j.carbpol.2005.03.019

Garg, U., Chauhan, S., Nagaich, U., & Jain, N. (2019). Current advances in chitosan nanoparticles based drug delivery and targeting. *Advanced Pharmaceutical Bulletin, 9*(2), 195–204. https://doi.org/10.15171/apb.2019.023. Tabriz University of Medical Sciences.

Gavini, E., Rassu, G., Ferraro, L., Beggiato, S., Alhalaweh, A., Velaga, S., … Dalpiaz, A. (2013). Influence of polymeric microcarriers on the in vivo intranasal uptake of an anti-migraine drug for brain targeting. *European Journal of Pharmaceutics and Biopharmaceutics, 83*, 174–183. https://doi.org/10.1016/j.ejpb.2012.10.010

Graf, B. A., Milbury, P. E., & Blumberg, J. B. (2005). Flavonols, flavones, flavanones, and human health: Epidemiological evidence. *Journal of Medicinal Food, 8*(3), 281–290. https://doi.org/10.1089/jmf.2005.8.281

Guo, T., Guo, Y., Gong, Y., Ji, J., Hao, S., Deng, J., & Wang, B. (2019). An enhanced charge-driven intranasal delivery of nicardipine attenuates brain injury after intracerebral hemorrhage. *International Journal of Pharmaceutics, 566*, 46–56. https://doi.org/10.1016/j.ijpharm.2019.05.050

Hao, C., Gao, L., Zhang, Y., Wang, W., Yu, G., Guan, H., et al. (2015). Acetylated Chitosan oligosaccharides act as antagonists against glutamate-induced PC12 cell death via Bcl-2/Bax Signal pathway. *Marine Drugs, 13*(3), Article 3. https://doi.org/10.3390/md13031267

Harilal, S., Jose, J., Parambi, D. G. T., Kumar, R., Mathew, G. E., & Uddin, M. S. (2019). Advancements in nanotherapeutics for Alzheimer's disease: Current perspectives. *Journal of Pharmacy and Pharmacology, 71*(9), 1370–1383. https://doi.org/10.1111/jphp.13132

Hersh, A. M., Alomari, S., & Tyler, B. M. (2022). Crossing the blood-brain barrier: Advances in nanoparticle technology for drug delivery in neuro-oncology. *International Journal of Molecular Sciences*, (8), 23. https://doi.org/10.3390/ijms23084153

Hinge, N. S., Kathuria, H., & Pandey, M. M. (2022). Engineering of structural and functional properties of nanotherapeutics and nanodiagnostics for intranasal brain targeting in Alzheimer's. *Applied Materials Today, 26*, Article 101303. https://doi.org/10.1016/j.apmt.2021.101303

Hou, Y., Dan, X., Babbar, M., Wei, Y., Hasselbalch, S. G., & Croteau, D. L. (2019). Ageing as a risk factor for neurodegenerative disease. *Nature Reviews Neurology, 15*(10), Article 10. https://doi.org/10.1038/s41582-019-0244-7

Hu, Y., Du, Y., Liu, N., Liu, X., Meng, T., Cheng, B., et al. (2015). Selective redox-responsive drug release in tumor cells mediated by Chitosan based glycolipid-like nanocarrier. *Journal of Controlled Release, 206*, 91–100. https://doi.org/10.1016/j.jconrel.2015.03.018

Huang, G., Liu, Y., & Chen, L. (2017). Chitosan and its derivatives as vehicles for drug delivery. *Drug Delivery, 24*(2), 108–113. https://doi.org/10.1080/10717544.2017.1399305

Imran, I., Javaid, S., Waheed, A., Rasool, M. F., Majeed, A., Samad, N., et al. (2021). Grewia asiatica berry juice diminishes anxiety, depression, and scopolamine-induced learning and memory impairment in behavioral experimental animal models. *Frontiers in Nutrition, 7*. https://doi.org/10.3389/fnut.2020.587367

Ishida, K., Yamamoto, M., Misawa, K., Nishimura, H., Misawa, K., Ota, N., et al. (2020). Coffee polyphenols prevent cognitive dysfunction and suppress amyloid β plaques in APP/PS2 transgenic mouse. *Neuroscience Research, 154*, 35–44. https://doi.org/10.1016/j.neures.2019.05.001

Iyer, M., Gomathi, M., Shanawaz, D., Vellingiri, B., & Keshavarao, S. (2016). Evaluation of clinical phenotypes associated with cytogenetic effects and Methylenetetrahydrofolate reductase (MTHFR) gene polymorphisms in Parkinson disease in Coimbatore region, South India. *Parkinsonism & Related Disorders, 22*, e170. https://doi.org/10.1016/j.parkreldis.2015.10.415

Jafernik, K., Ładniak, A., Blicharska, E., Czarnek, K., Ekiert, H., & Wiącek, A. E. (2023). Chitosan-based nanoparticles as effective drug delivery systems—a review. *Molecules, 28*(4), 1963. https://doi.org/10.3390/molecules28041963. Multidisciplinary Digital Publishing Institute.

Jayaramayya, K., Iyer, M., Venkatesan, D., Balasubramanian, V., Narayanasamy, A., & Subramaniam, M. D. (2020). Unraveling correlative roles of dopamine transporter (DAT) and Parkin in Parkinson's disease (PD) – A road to discovery? *Brain Research Bulletin, 157*, 169–179. https://doi.org/10.1016/j.brainresbull.2020.02.001

Je, J. Y., & Kim, S. K. (2005). Water-soluble chitosan derivatives as a BACE1 inhibitor. *Bioorganic & Medicinal Chemistry, 13*(23), 6551–6555. https://doi.org/10.1016/j.bmc.2005.07.004

Jha, A., Ghormade, V., Kolge, H., & Paknikar, K. M. (2019). Dual effect of chitosan-based nanoparticles on the inhibition of β-amyloid peptide aggregation and disintegration of the preformed fibrils. *Journal of Materials Chemistry B, 7*(21), Article 21. https://doi.org/10.1039/C9TB00162J. Article.

Jin, Y., Hu, X., Zhang, Y., & Liu, T. (2016). Studies on the purification of polysaccharides separated from Tremella fuciformis and their neuroprotective effect. *Molecular Medicine Reports, 13*(5), 3985–3992. https://doi.org/10.3892/mmr.2016.5026

Jung, J., & Zhao, Y. (2011). Characteristics of deacetylation and depolymerization of β-chitin from jumbo squid (Dosidicus gigas) pens. *Carbohydrate Research, 346*, 1876–1884. https://doi.org/10.1016/j.carres.2011.05.021

Kaur, S., & Dhillon, G. S. (2014). The versatile biopolymer chitosan: Potential sources, evaluation of extraction methods and applications. *Critical Reviews in Microbiology, 40*(2), 155–175. https://doi.org/10.3109/1040841X.2013.770385

Khalaf, E. M., Abood, N. A., Atta, R. Z., Ramírez-Coronel, A. A., Alazragi, R., Parra, R. M. R., et al. (2023). Recent progressions in biomedical and pharmaceutical applications of chitosan nanoparticles: A comprehensive review. *International Journal of Biological Macromolecules, 231*, Article 123354. https://doi.org/10.1016/j.ijbiomac.2023.123354

Khiralla, G., Elhariry, H., & Selim, S. (2020). Chitosan-stabilized selenium nanoparticles attenuate acrylamide-induced brain injury in rats. *Journal of Food Biochemistry, 44*. https://doi.org/10.1111/jfbc.13413

Kim, J. H., He, M. T., Kim, M. J., Yang, C. Y., Shin, Y. S., Yokozawa, T., et al. (2019). Safflower (Carthamus tinctorius L.) seed attenuates memory impairment induced by scopolamine in mice via regulation of cholinergic dysfunction and oxidative stress. *Food & Function, 10*(6), 3650–3659. https://doi.org/10.1039/C9FO00615J

Kim, J. H., Lee, J., Lee, S., & Cho, E. J. (2016). Quercetin and quercetin-3-β-D-glucoside improve cognitive and memory function in Alzheimer's disease mouse. *Applied Biological Chemistry, 59*(5), Article 5. https://doi.org/10.1007/s13765-016-0217-0. Article.

Kim, M. S., Sung, M. J., Seo, S. B., Yoo, S. J., Lim, W. K., & Kim, H. M. (2002). Water-soluble Chitosan inhibits the production of pro-inflammatory cytokine in human astrocytoma cells activated by amyloid β peptide and interleukin-1β. *Neuroscience Letters, 321*(1), 105–109. https://doi.org/10.1016/S0304-3940(02)00066-6

Kim, S., Nishimoto, S. K., Bumgardner, J. D., Haggard, W. O., Gaber, M. W., & Yang, Y. (2010). A chitosan/β-glycerophosphate thermo-sensitive gel for the delivery of ellagic acid for the treatment of brain cancer. *Biomaterials, 31*, 4157–4166. https://doi.org/10.1016/j.biomaterials.2010.01.139

Kołodziejska, M., Jankowska, K., Klak, M., & Wszoła, M. (2021). Chitosan as an underrated polymer in modern tissue engineering. *Nanomaterials, 11*(11). https://doi.org/10.3390/nano11113019. MDPI.

Koo, H. N., Jeong, H. J., Hong, S. H., Choi, J. H., An, N. H., & Kim, H. M. (2002). High molecular weight water-soluble Chitosan protects against apoptosis induced by serum starvation in human astrocytes. *The Journal of Nutritional Biochemistry, 13*(4), 245–249. https://doi.org/10.1016/S0955-2863(01)00218-2

Kumar, M. N. V. R., Muzzarelli, R. A. A., Muzzarelli, C., Sashiwa, H., & Domb, A. J. (2004). Chitosan chemistry and pharmaceutical perspectives. *Chemical Reviews, 104*(12), 6017–6084. https://doi.org/10.1021/cr030441b

Kurita, K., Kaji, Y., Mori, T., & Nishiyama, Y. (2000). Enzymatic degradation of β-chitin: Susceptibility and the influence of deacetylation. *Carbohydrate Polymers, 42*(1), 19–21. https://doi.org/10.1016/S0144-8617(99)00127-7

Lee, A. Y., Hwang, B. R., Lee, M. H., Lee, S., & Cho, E. J. (2016). KoreaMed synapse. *Nutrition Research and Practice, 10*(3), 274–281. https://doi.org/10.4162/nrp.2016.10.3.274

Lemieszek, M. K., Nunes, F. M., Cardoso, C., Marques, G., & Rzeski, W. (2018). Neuroprotective properties of Cantharellus cibarius polysaccharide fractions in different *In vitro* models of neurodegeneration. *Carbohydrate Polymers, 197*, 598–607. https://doi.org/10.1016/j.carbpol.2018.06.038

Li, G. F., Wang, J. C., Feng, X. M., Liu, Z. D., Jiang, C. Y., & Yang, J. D. (2015). Preparation and testing of quaternized chitosan nanoparticles as gene delivery vehicles. *Applied Biochemistry and Biotechnology, 175*(7), 3244–3257. https://doi.org/10.1007/s12010-015-1483-8

Li, J., Cai, C., Li, J., Li, J., Li, J., Sun, T., et al. (2018). Chitosan-based nanomaterials for drug delivery. *Molecules, 23*(10). https://doi.org/10.3390/molecules23102661

Liu, S., Sun, J., Yu, L., Zhang, C., Bi, J., Zhu, F., et al. (2012). Extraction and characterization of chitin from the beetle holotrichia parallela motschulsky. *Molecules, 17*(4), Article 4. https://doi.org/10.3390/molecules17044604

Lu, P., Mamiya, T., Lu, L. L., Mouri, A., Niwa, M., Hiramatsu, M., et al. (2009). Silibinin attenuates amyloid β25–35 peptide-induced memory impairments: Implication of inducible nitric-oxide synthase and tumor necrosis factor-α in mice. *Journal of Pharmacology and Experimental Therapeutics, 331*(1), 319–326. https://doi.org/10.1124/jpet.109.155069

Lü, S., Liu, M., & Ni, B. (2010). An injectable oxidized carboxymethylcellulose/N-succinyl-chitosan hydrogel system for protein delivery. *Chemical Engineering Journal, 160*(2), 779–787. https://doi.org/10.1016/j.cej.2010.03.072

Luo, L. J., Nguyen, D. D., & Lai, J. Y. (2020). Benzoic acid derivative-modified chitosan-g-poly(N-isopropylacrylamide): Methoxylation effects and pharmacological treatments of Glaucoma-related neurodegeneration. *Journal of Controlled Release, 317*, 246–258. https://doi.org/10.1016/j.jconrel.2019.11.038

Malhotra, M., Tomaro-Duchesneau, C., & Prakash, S. (2013). Synthesis of TAT peptide-tagged PEGylated chitosan nanoparticles for siRNA delivery targeting neurodegenerative diseases. *Biomaterials, 34*(4), 80–1270. https://doi.org/10.1016/j.biomaterials.2012.10.013

M. Ways, T. M., Lau, W. M., & Khutoryanskiy, V. V. (2018). Chitosan and its derivatives for application in mucoadhesive drug delivery systems. *Polymers, 10*(3), Article 3. https://doi.org/10.3390/polym10030267

Ma, Z., Wang, W., Wu, Y., He, Y., & Wu, T. (2014). Oxidative degradation of Chitosan to the low molecular water-soluble Chitosan over peroxotungstate as chemical scissors. *PloS One, 9*(6), Article e100743. https://doi.org/10.1371/journal.pone.0100743. –e100743PubMed.

Manni, L., Ghorbel-Bellaaj, O., Jellouli, K., Younes, I., & Nasri, M. (2010). Extraction and characterization of Chitin, Chitosan, and protein hydrolysates prepared from shrimp waste by treatment with crude protease from Bacillus cereus SV1. *Applied Biochemistry and Biotechnology, 162*(2), 345–357. https://doi.org/10.1007/s12010-009-8846-y

Marei, N. H., El-Samie, E. A., Salah, T., Saad, G. R., & Elwahy, A. H. M. (2016). Isolation and characterization of Chitosan from different local insects in Egypt. *International Journal of Biological Macromolecules, 82*, 871–877. https://doi.org/10.1016/j.ijbiomac.2015.10.024

Meng, X., Fu, M., Wang, S., Chen, W., Wang, J., & Zhang, N. (2021). Naringin ameliorates memory deficits and exerts neuroprotective effects in a mouse model of Alzheimer's disease by regulating multiple metabolic pathways. *Molecular Medicine Reports, 23*(5), 1–13. https://doi.org/10.3892/mmr.2021.11971

Modak, C., Jha, A., Sharma, N., & Kumar, A. (2021). Chitosan derivatives: A suggestive evaluation for novel inhibitor discovery against wild type and variants of SARS-CoV-2 virus. *International Journal of Biological Macromolecules, 187*, 492–512. https://doi.org/10.1016/j.ijbiomac.2021.07.144

Mohammed, M. H., Williams, P. A., & Tverezovskaya, O. (2013). Extraction of Chitin from prawn shells and conversion to low molecular mass chitosan. *Food Hydrocolloids, 31*(2), 166–171. https://doi.org/10.1016/j.foodhyd.2012.10.021

Moura, C. M., Moura, J. M., Soares, N. M., & Pinto, L. A. A. (2011). Evaluation of molar weight and deacetylation degree of Chitosan during chitin deacetylation reaction: Used to produce biofilm. *Chemical Engineering and Processing: Process Intensification, 50*(4), 351–355. https://doi.org/10.1016/j.cep.2011.03.003

Mucha, M., & Pawlak, A. (2022). Complex study on chitosan degradability. *Polimery, 47*(7–8), 509–516.

Mukherjee, A. G., Wanjari, U. R., & Nagarajan, D. (2022). Letrozole: Pharmacology, toxicity and potential therapeutic effects. *Life Sciences, 310*, Article 121074. https://doi.org/10.1016/j.lfs.2022.121074

Muxika, A., Etxabide, A., Uranga, J., Guerrero, P., & de la Caba, K. (2017). Chitosan as a bioactive polymer: Processing, properties and applications. *International Journal of Biological Macromolecules, 105*, 1358–1368. https://doi.org/10.1016/j.ijbiomac.2017.07.087

Misra, A., Ganesh, S., & Shahiwala, A. (2003). Drug delivery to the central nervous system: A review. *Journal of Pharmaceutical Sciences, 6*(2), 73–252.

Muzzarelli, R. (1973). Natural chelating polymers. Alginic acid, chitin and Chitosan. Natural Chelating Polymers. Alginic Acid, Chitin and Chitosan.

Nakajima, A., Aoyama, Y., Shin, E. J., Nam, Y., Kim, H. C., Nagai, T., et al. (2015). Nobiletin, a citrus flavonoid, improves cognitive impairment and reduces soluble Aβ levels in a triple transgenic mouse model of Alzheimer's disease (3XTg-AD). *Behavioural Brain Research, 289*, 69–77. https://doi.org/10.1016/j.bbr.2015.04.028

Nazari, L., Komaki, S., Salehi, I., Raoufi, S., Golipoor, Z., Kourosh-Arami, M., et al. (2022). Investigation of the protective effects of lutein on memory and learning using behavioral methods in a male rat model of Alzheimer's disease. *Journal of Functional Foods, 99*, Article 105319. https://doi.org/10.1016/j.jff.2022.105319

Olatunji, O. J., Feng, Y., Olatunji, O. O., Tang, J., Wei, Y., Ouyang, Z., et al. (2016). Polysaccharides purified from Cordyceps cicadae protects PC12 cells against glutamate-induced oxidative damage. *Carbohydrate Polymers, 153*, 187–195. https://doi.org/10.1016/j.carbpol.2016.06.108

Parikh, A., Kathawala, K., Song, Y., Zhou, X. F., & Garg, S. (2018). Curcumin-loaded self-nanomicellizing solid dispersion system: Part I: Development, optimization, characterization, and oral bioavailability. *Drug Delivery and Translational Research, 8*(5), 1389–1405. https://doi.org/10.1007/s13346-018-0543-3

Patel, M. M., & Patel, B. M. (2017). Crossing the blood–brain barrier: Recent advances in drug delivery to the brain. *CNS drugs, 31*(2), 109–133. https://doi.org/10.1007/s40263-016-0405-9

Pochanavanich, P., & Suntornsuk, W. (2002). Fungal chitosan production and its characterization. *Letters in Applied Microbiology, 35*(1), 17–21. https://doi.org/10.1046/j.1472-765X.2002.01118.x

Rajamanickam, G., & Manju, S. L. (2023). Formulation and characterization of chitosan nanoparticles loaded with neuroprotective flavonoid from Phyllanthus niruri Linn. *Macromolecular Research, 31*(1), 13–24. https://doi.org/10.1007/s13233-023-00114-z

Reddy, A. P., Ravichandran, J., & Carkaci-Salli, N. (2020). Neural regeneration therapies for Alzheimer's and Parkinson's disease-related disorders. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 1866*(4), Article 165506. https://doi.org/10.1016/j.bbadis.2019.06.020

Reddy, P. H., Manczak, M., Yin, X., Grady, M. C., Mitchell, A., Tonk, S., et al. (2018). Protective effects of Indian spice curcumin against Amyloid-β in Alzheimer's disease. *Journal of Alzheimer's Disease, 61*(3), 843–866. https://doi.org/10.3233/JAD-170512

Renugalakshmi, A., Sekar Vinothkumar, T., & Kandaswamy, D. (2011). Nanodrug delivery systems in dentistry: A review on current status and future perspectives. *Current Drug Delivery, 8*(5), 586–594. https://doi.org/10.2174/156720111796642336

Revathi, G., Elavarasi, S., Saravanan, K., Ashokkumar, M., & Egbuna, C. (2023). Greater efficiency of polyherbal drug encapsulated biosynthesized chitosan nano-biopolymer on diabetes and its complications. *International Journal of Biological Macromolecules, 240*, Article 124445. https://doi.org/10.1016/j.ijbiomac.2023.124445

Rezaii, M., Oryan, S., & Javeri, A. (2019). Curcumin nanoparticles incorporated collagen-chitosan scaffold promotes cutaneous wound healing through regulation of TGF-β1/Smad7 gene expression. *Materials Science and Engineering: C, 98*, 347–357. https://doi.org/10.1016/j.msec.2018.12.143

Saboktakin, M. R., Tabatabaie, R. M., Maharramov, A., & Ramazanov, M. A. (2011). Synthesis and characterization of pH-dependent glycol chitosan and dextran sulfate nanoparticles for effective brain cancer treatment. *International Journal of Biological Macromolecules, 49*, 747–751. https://doi.org/10.1016/j.ijbiomac.2011.07.006

Sánchez-López, E., Ettcheto, M., Egea, M. A., Espina, M., Cano, A., & Calpena, A. C. (2018). Memantine loaded PLGA PEGylated nanoparticles for Alzheimer's disease: *In vitro* and *in vivo* characterization. *Journal of Nanobiotechnology, 16*(1), 32. https://doi.org/10.1186/s12951-018-0356-z

Sanchez-Ramos, J., Song, S., Kong, X., Foroutan, P., Martinez, G., Dominguez-Viqueria, W., … Sava, V. (2018). Chitosan-Mangafodipir nanoparticles designed for intranasal delivery of siRNA and DNA to brain. *Journal of Drug Delivery Science and Technology, 43*, 453–460. https://doi.org/10.1016/j.jddst.2017.11.013

Sarvaiya, J., & Agrawal, Y. K. (2015). Chitosan as a suitable nanocarrier material for anti-Alzheimer drug delivery. *International Journal of Biological Macromolecules, 72*, 454–465. https://doi.org/10.1016/j.ijbiomac.2014.08.052

Sasikalaa, K., SureshKumar, S., Balamuralikrishnana, B., Aruna, M., Karthickkumar, A., & Ahmad, A. M. (2016). Cytogenetic analysis and screening of ApoE and neurotransmitters in Alzheimer's patients in Tamil Nadu population. *International Journal of Human Genetics, 16*(3–4), 107–115. https://doi.org/10.1080/09723757.2016.11886285

Shahidi, F., & Synowiecki, J. (2002). *Isolation and characterization of nutrients and value-added products from snow crab (Chionoecetes opilio) and shrimp (Pandalus borealis) processing discards (world)*. May 1. ACS Publications; American Chemical Society. https://doi.org/10.1021/jf00008a032.

Shayganfard, M. (2022). A review on Chitosan in drug delivery for treatment of neurological and psychiatric disorders. *Current Pharmaceutical Biotechnology, 23*(4), 538–551. https://doi.org/10.2174/1389201022666210622111028

Shukla, R., Pandey, V., Vadnere, G. P., & Lodhi, S. (2019). Chapter 18—Role of flavonoids in management of inflammatory disorders. R. & R. Watson & V. R. Preedy (Eds.). *Bioactive food as dietary interventions for arthritis and related inflammatory diseases* (2nd ed., pp. 293–322). Academic Press. https://doi.org/10.1016/B978-0-12-813820-5.00018-0.

Singh, G., Sharma, M., Kumar, G. A., Rao, N. G., Prasad, K., Mathur, P., et al. (2021). The burden of neurological disorders across the states of India: The Global Burden of Disease Study 1990–2019. *The Lancet Global Health, 9*(8), e1129–e1144. https://doi.org/10.1016/S2214-109X(21)00164-9

Stanzione, P., & Tropepi, D. (2011). Drugs and clinical trials in neurodegenerative diseases. *Annali Dell'Istituto Superiore Di Sanità, 47*, 49–54. https://doi.org/10.4415/ANN_11_01_11

Sun, X., Li, L., Dong, Q. X., Zhu, J., Huang, Y., Hou, S., et al. (2021). Rutin prevents tau pathology and neuroinflammation in a mouse model of Alzheimer's disease. *Journal of Neuroinflammation, 18*(1), 131. https://doi.org/10.1186/s12974-021-02182-3

Sung, Y. K., & Kim, S. W. (2020). Recent advances in polymeric drug delivery systems. *Biomaterials Research, 24*(1), 12. https://doi.org/10.1186/s40824-020-00190-7

Szebeni, J. (2012). Hemocompatibility testing for nanomedicines and biologicals: predictive assays for complement mediated infusion reactions. European Journal of Nanomedicine, 4(1), 3353. 10.1515/ejnm-2012-0002.

Szymańska, E., & Winnicka, K. (2015). Stability of Chitosan—a challenge for pharmaceutical and biomedical applications. *Marine Drugs, 13*(4), 1819–1846. https://doi.org/10.3390/md13041819

Tang, W., Wang, J., Hou, H., Li, Y., Wang, J., Fu, J., et al. (2023). Review: Application of Chitosan and its derivatives in medical materials. *International Journal of Biological Macromolecules, 240*, Article 124398. https://doi.org/10.1016/j.ijbiomac.2023.124398

Tian, B., & Liu, J. (2023). Smart stimuli-responsive chitosan hydrogel for drug delivery: A review. *International Journal of Biological Macromolecules, 235*, Article 123902. https://doi.org/10.1016/j.ijbiomac.2023.123902

Torres, F. G., Troncoso, O. P., Pisani, A., Gatto, F., & Bardi, G. (2019). Natural polysaccharide nanomaterials: An overview of their immunological properties. *International Journal of Molecular Sciences, 20*(20), Article 20. https://doi.org/10.3390/ijms20205092

Ullah, R., Ali, G., Baseer, A., Irum Khan, S., Akram, M., Khan, S., et al. (2022). Tannic acid inhibits lipopolysaccharide-induced cognitive impairment in adult mice by targeting multiple pathological features. *International Immunopharmacology, 110*, Article 108970. https://doi.org/10.1016/j.intimp.2022.108970

Vellingiri, B., Suriyanarayanan, A., Selvaraj, P., Abraham, K. S., Pasha, Md. Y., Winster, H., et al. (2022). Role of heavy metals (copper (Cu), arsenic (As), cadmium (Cd), iron (Fe) and lithium (Li)) induced neurotoxicity. *Chemosphere, 301*, Article 134625. https://doi.org/10.1016/j.chemosphere.2022.134625

Venkatesan, D., Iyer, M., S, R. W., G, L., & Vellingiri, B. (2021). The association between multiple risk factors, clinical correlations and molecular insights in Parkinson's disease patients from Tamil Nadu population, India. *Neuroscience Letters, 755*, Article 135903. https://doi.org/10.1016/j.neulet.2021.135903

Venugopal, A., Venkatesan, D., Bharathi, G., & Vellingiri, B. (2018). Screening of ApoE genotypic frequency and analysis of neurotransmitter levels in Alzheimer's patients of Coimbatore population. *Parkinsonism & Related Disorders, 46*, e47. https://doi.org/10.1016/j.parkreldis.2017.11.160

Victor, R., de, S., Santos, A. M., da, C., de Sousa, B. V., Neves, G., et al. (2020). A review on Chitosan's uses as biomaterial: Tissue engineering, drug delivery systems and cancer treatment. *Materials, 13*(21), 1–71. https://doi.org/10.3390/ma13214995. Multidisciplinary Digital Publishing Institute (MDPI).

Wang, D., Liu, L., Li, S., & Wang, C. (2018). Effects of paeoniflorin on neurobehavior, oxidative stress, brain insulin signaling, and synaptic alterations in intracerebroventricular streptozotocin-induced cognitive impairment in mice. *Physiology & Behavior, 191*, 12–20. https://doi.org/10.1016/j.physbeh.2018.03.016

Wang, H., Zhang, F., Xu, Y., Fu, H., Wang, X., Wang, L., et al. (2020). The phosphodiesterase-4 inhibitor roflumilast, a potential treatment for the comorbidity of memory loss and depression in Alzheimer's Disease: A Preclinical study in APP/PS1 transgenic mice. *International Journal of Neuropsychopharmacology, 23*(10), 700–711. https://doi.org/10.1093/ijnp/pyaa048

Wang, X., Miao, J., Yan, C., Ge, R., Liang, T., Liu, E., et al. (2016). Chitosan attenuates dibutyltin-induced apoptosis in PC12 cells through inhibition of the mitochondria-dependent pathway. *Carbohydrate Polymers, 151*, 996–1005. https://doi.org/10.1016/j.carbpol.2016.06.053

Wang, Z. H., Wang, Z. Y., Sun, C. S., Wang, C. Y., Jiang, T. Y., & Wang, S. L. (2010). Trimethylated chitosan-conjugated PLGA nanoparticles for the delivery of drugs to the brain. *Biomaterials, 31*(5), 908–915. https://doi.org/10.1016/j.biomaterials.2009.09.104

Wei, S., Xu, P., Yao, Z., Cui, X., Lei, X., Li, L., et al. (2021). A composite hydrogel with co-delivery of antimicrobial peptides and platelet-rich plasma to enhance healing of infected wounds in diabetes. *Acta Biomaterialia, 124*, 205–218. https://doi.org/10.1016/j.actbio.2021.01.046

Widhiantara, I. G., Permatasari, A. A. A. P., Rosiana, I. W., Wiradana, P. A., Widiastini, L. P., & Jawi, I. M. (2021). Antihypercholesterolemic and antioxidant effects of blumea balsamifera L. leaf extracts to maintain luteinizing hormone secretion in rats induced by high-cholesterol diets. *The Indonesian Biomedical Journal, 13*(4), Article 4. https://doi.org/10.18585/inabj.v13i4.1694

Wilson, B., Samanta, M. K., Santhi, K., Kumar, K. P. S., Ramasamy, M., & Suresh, B. (2010). Chitosan nanoparticles as a new delivery system for the anti-Alzheimer drug tacrine. *Nanomedicine: Nanotechnology, Biology and Medicine, 6*(1), 144–152. https://doi.org/10.1016/j.nano.2009.04.001

Wysokowski, M., Petrenko, I., Stelling, A. L., Stawski, D., Jesionowski, T., & Ehrlich, H. (2015). Poriferan Chitin as a versatile template for extreme biomimetics. *Polymers, 7*(2), Article 2. https://doi.org/10.3390/polym7020235

Xu, Y., Asghar, S., Yang, L., Li, H., Wang, Z., Ping, Q., & Xiao, Y. (2017). Lactoferrin-coated polysaccharide nanoparticles based on chitosan hydrochloride/hyaluronic acid/PEG for treating brain glioma. *Carbohydrate Polymers, 157*, 419–428. https://doi.org/10.1016/j.carbpol.2016.09.085

Xue, Y., Wang, N., Zeng, Z., Huang, J., Xiang, Z., & Guan, Y. Q. (2020). Neuroprotective effect of chitosan nanoparticle gene delivery system grafted with acteoside (ACT) in Parkinson's disease models. *Journal of Materials Science & Technology, 43*, 197–207. https://doi.org/10.1016/j.jmst.2019.10.013

Yadav, M., Parle, M., Sharma, N., Dhingra, S., Raina, N., & Jindal, D. K. (2017). Brain targeted oral delivery of doxycycline hydrochloride encapsulated Tween 80 coated chitosan nanoparticles against ketamine induced psychosis: Behavioral, biochemical, neurochemical and histological alterations in mice. *Drug Delivery, 24*(1), 1429–1440. https://doi.org/10.1080/10717544.2017.1377315

Yang, L., Gao, S., Asghar, S., Liu, G., Song, J., Wang, X., … Xiao, Y. (2015). Hyaluronic acid/chitosan nanoparticles for delivery of curcuminoid and its in vitro evaluation in glioma cells. *International Journal of Biological Macromolecules, 72*, 1391–1401. https://doi.org/10.1016/j.ijbiomac.2014.10.039

Yang, L., Wang, Y., Zheng, G., Li, Z., & Mei, J. (2023). Resveratrol-loaded selenium/chitosan nano-flowers alleviate glucolipid metabolism disorder-associated cognitive impairment in Alzheimer's disease. *International Journal of Biological Macromolecules, 239*, Article 124316. https://doi.org/10.1016/j.ijbiomac.2023.124316

Zargani, M., Ramirez-Campillo, R., & Arabzadeh, E. (2023). Swimming and L-arginine loaded chitosan nanoparticles ameliorates aging-induced neuron atrophy, autophagy marker LC3, GABA and BDNF-TrkB pathway in the spinal cord of rats. *Pflugers Archiv European Journal of Physiology*, 1–15. https://doi.org/10.1007/s00424-023-02795-y

Zargar, V., Asghari, M., & Dashti, A. (2015). A review on Chitin and Chitosan polymers: Structure, chemistry, solubility, derivatives, and applications. *ChemBioEng Reviews, 2*(3), 204–226. https://doi.org/10.1002/cben.201400025

Zeissler, M. L., Eastwood, J., McCorry, K., Hanemann, C. O., Zajicek, J. P., & Carroll, C. B. (2016). Delta-9-tetrahydrocannabinol protects against MPP+ toxicity in SH-SY5Y

cells by restoring proteins involved in mitochondrial biogenesis. *Oncotarget, 7*(29), Article 29. https://doi.org/10.18632/oncotarget.10314. Article.

Zhai, X., Zhang, C., Stoll, S., Ren, F., & Leng, X. (2017). Antioxidant capacities of the selenium nanoparticles stabilized by Chitosan. *Journal of Nanobiotechnology, 15*. https://doi.org/10.1186/s12951-016-0243-4

Zhang, J., Xia, W., Liu, P., Cheng, Q., Tahi, T., Gu, W., et al. (2010). Chitosan modification and pharmaceutical/biomedical applications. *Marine Drugs, 8*(7), Article 7. https://doi.org/10.3390/md8071962

Zhao, D., Yu, S., Sun, B., Gao, S., Guo, S., & Zhao, K. (2018). Biomedical applications of Chitosan and its derivative nanoparticles. *Polymers, 10*(4). https://doi.org/10.3390/polym10040462. Multidisciplinary Digital Publishing Institute (MDPI).

Zhou, S., Yang, Y., Gu, X., & Ding, F. (2008). Chitooligosaccharides protect cultured hippocampal neurons against glutamate-induced neurotoxicity. *Neuroscience Letters, 444*(3), 270–274. https://doi.org/10.1016/j.neulet.2008.08.040