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Phytonanoparticles for the treatment of Alzheimer's disease: A review

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Abstract

Alzheimer's disease, (AD) is a neurodegenerative disease characterized by cognitive dysfunction and is an age-related disease. The neuropathology of AD is β-amyloid (Aβ) peptide in the brain and causes neurofibrillary tangles. The acetylcholine level is reduced in the hippocampus and acetylcholinesterase (AChE) is enhanced causing memory deterioration. Oxidative damage is one of the major cellular impacts affected during AD condition. Plant derived polyphenols are the compounds which are having remarkable effect of free radical scavenging effect and AChE inhibitory effect in brain. The treatment with phytocompounds were highly effective for neuroprotection and systematically regulates the brain organic balance. The limitations of phytocompounds to penetrate the blood brain barrier is majorly surpassed by the novel drug delivery systems such as nanoparticles. Nanoformulations of phytocompounds have a greatest potential for the target delivery of drugs to the brain and have maximal therapeutic effect. This review states the remarkable impacts of selected phytonanoparticles for the treatment of AD.

1. Introduction

Neurodegenerative disorders lead to cognitive decline caused by accumulation of neurotoxic peptides associated with physiological stress. In Alzheimer's disease (AD), stress escalates the cortisol, diminishing cognition and affecting emotion and social health. Worldwide, 46.8 million people are affected by dementia (Gheidari and Bayat, 2022). Current Alzheimer's treatment, acetylcholinesterase enzyme inhibitors delay Alzheimer's from progressing and it can temporarily reduce dementia symptoms (Kumar *et al.*, 2018). Despite the low bioavailability profile, the currently available drugs such as acetylcholinesterase (AChE) inhibitors (donepezil, tacrine and rivastigmine) are only affording symptomatic control (Cummings *et al.*, 2020). These drugs also alter the brain neurotransmitters and cause adverse effects such as insomnia, anorexia, dyspepsia, muscle cramps and asthenia. At present, there is a worldwide effort to find better ways to treat the disease, delay its onset, and prevent it from developing. As a preventive measure, basic quality of life enhancement with nutritious food habits balanced with fruits and natural products enhances neuroprotection (Hanish Singh Jayasingh *et al.*, 2020). Currently, there is no cure for AD. Despite symptomatic treatments, any drug or any chemical entity which controls the disease progression value adds the therapeutic management of AD and makes life better for millions of people living with AD. Natural antioxidant compounds are widely considered promising agents for the treatment of neurodegenerative diseases with the least adverse effects. Plant-derived bioactive molecules include enzymes, amino acids, vitamins, essential oils, minerals, fibres and polyphenols. Polyphenolic compounds with neuroprotective and antioxidant potential are considered crucial therapeutic drugs and supplements to prevent memory loss. Naturally occurring biomolecules of plant origin are very helpful in managing and treating many non-communicable disease conditions (Sarubbo *et al.*, 2018). Especially polyphenols are among the highest therapeutically active components. Polyphenols such as resveratrol, quercetin epigallocatechin-3-gallate and curcuminare the widely studied phytocompounds and are described to be effective for neurodegenerative diseases (Sawikr *et al.*, 2017). Formulation design and drug targetability to the brain are the essential key factors for the phytomolecules due to their limitation in target site concentration. For the neurodegenerative disease drug targeting with the nanomedicine, formulation gained much attention. Nanoparticle formulation is the most opted formulation to target brain delivery, and it has novel properties due to their size, distribution ability and morphological nature. Nanoformulations with active components of phytoconstituents were highly therapeutically active due to their direct target distribution. Many phytocomponents (curcumin, resveratrol and luteolin) in the form of nanoparticles were studied by researchers, and it revealed that the formulation exhibited optimised therapeutic effect and high drug concentration with minimal or negligible adverse drug effects (Paramanick *et al.*, 2022).

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2. Nanoparticles for treatment of neurodegeneration

The nanotechnological dexterity in medicine (nanomedicine) is the fastest-growing diagnostic and therapeutic aid. Nanomedicine precisely enhanced the diagnosis and treatment of various diseases. In nanomedicine, many formulations were pharmacologically studied and reported. This included nanoparticles, polymeric micelles, solid lipid nanoparticles, dendrimers, liposomes, flexible liposomes (transferosomes), immunoliposomes, nanoemulsion, nanosuspension, carbon nanotubes, antibodies and their conjugates and viral vectors. In brain drug delivery, the nanoparticles play a crucial role and they are the most commonly used drug delivery system for the delivery of anticancer and other drugs for the treatment of neurodegeneration. Nanoparticles (NPs) have shown remarkable outcomes to target drugs for the treatment of neurodegenerative disease (Paramanick *et al.*, 2022). NPs minimise the therapeutic dose, thereby reducing the adverse effect and also reported to have less frequency in administration. These altogether improve patient compliance and exerts optimised therapy. The vital physical properties that play for the effect of nanoparticles are their size and surface properties such as charge, hydrophilicity and hydrophobicity. These are the key factors for the interaction of nanoparticles with the cellular surface and the subsequent internalisation into the target cells. NPs, after administration, get accumulate in the brain capillaries. This retention and adsorption on the capillary endothelial cells escalate the concentration gradient to improve the penetration of NPs containing drugs. This increases the bioavailability and exerts the pharmacological action due to the high concentration in the organ compartment.

3. Phytonanoparticles

Bioactive polyphenolic compounds have been studied for neurodegeneration which are designed as nanoparticles.

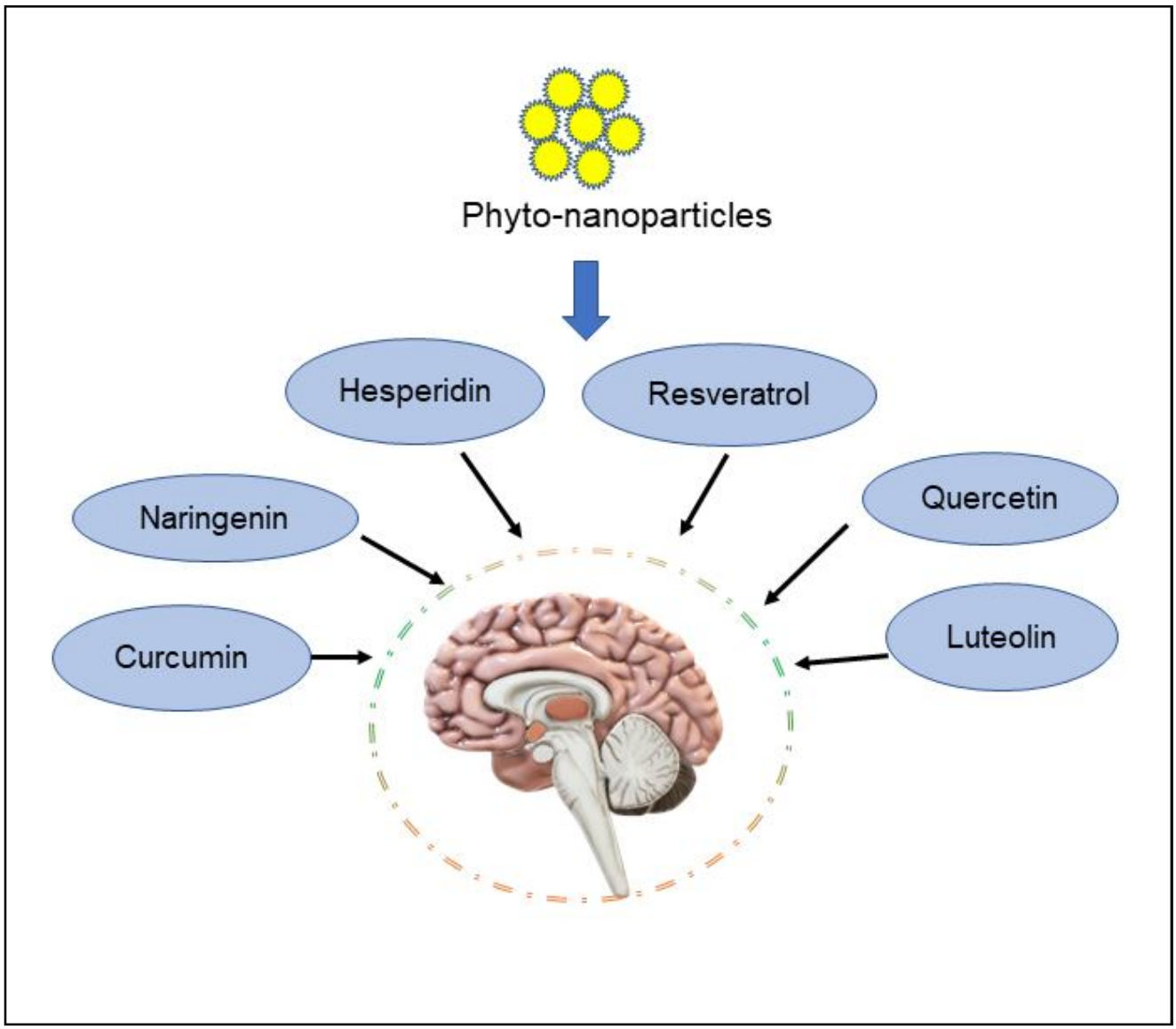

Figure 1: The phytonanoparticles which are studied for Alzheimer's type of neurodegeneration.

3.1 Resveratrol

Resveratrol (3, 5, 42 -trihydroxy-trans-stilbene) is a polyphenol that has wide therapeutic benefits and has been explored for treating neurodegenerative diseases and other diseases. Resveratrol is a compound mainly present in grape peel and more than 70 different plant species (Gheidari and Bayat, 2022). Earlier studies on resveratrol indicated many pharmacotherapeutic activities such as anti-inflammatory, antioxidant cardioprotective and neuroprotective effects. Trans-resveratrol (Figure 2 b) is highly therapeutically active than cis-resveratrol (Figure 2 a).

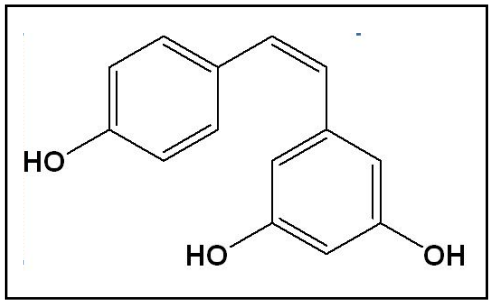

Figure 2(a): cis-Resveratrol.

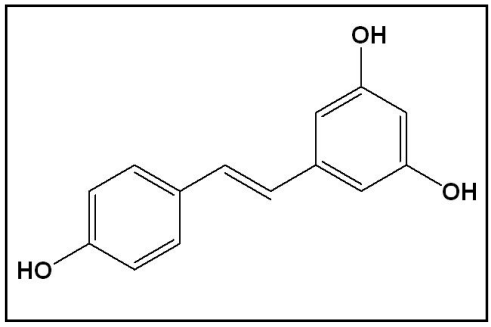

Figure 2(b): trans-Reveratrol.

Resveratrol is prepared in the form of solid lipid nanoparticles by high shear homogenisation technique and evaluated for its neuroprotective effect. Resveratrol in solid lipid nanoparticles was found to be effective in neuroprotection. Formulated resveratrol selenium nanoparticles were evaluated in Alzheimer's dementia-induced animal models. In this study, aluminium chloride (100 mg/kg/day) was administered for AD induction, and the animals were treated with resveratrol nanoparticles. It is found that the resveratrol nanoformulation has an excellent impact on free radical scavenging property in the brain; it attenuated Aβ aggregation and promoted the clearance of Aβ peptide. It is also found that the treatment activated the phosphatidylinositol 3 kinase (PI3K) and controlled the 'tau' hyperphosphorylation through inhibition of glycogen synthase kinase 3 beta (GSK-3β). Resveratrol selenium nanoparticles also inhibited the inflammatory events and downregulated the expression of signal transduction activator (STAT3) and interleukin-1β (IL-1β) levels in the brain. It also stimulated the expression of sirtuin-1 (SIRT1) and improved essential neurite growth. This indicated that resveratrol in nanoformulations effectively works against AD type of dementia by improving the neurocognitive properties (Abozaid *et al.*, 2022). In a study using ICR mice treated with aluminium chloride and D-galactose as an AD model, selenium nanoparticles improved spatial memory and alleviate cerebral atrophy. It was suggested that resveratrol selenium nanoparticles protect the central nervous system by normalizing the levels of neurotransmitters (Li *et al.*, 2021).

3.2 Quercetin

The sources of quercetin are vegetables, fruits and nuts and is a nutritional diet flavonoid (Figure 3). It is also in the form of polyphenolic flavonoid in figs, grapes, apples, red onion, lettuce, tomato,berries and walnuts.

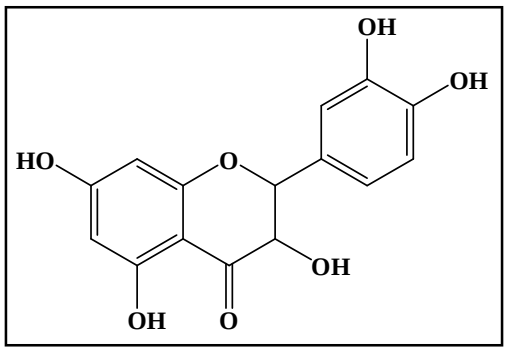

Figure 3: Quercetin.

It has very good health benefits as an antioxidant and has therapeutic benefits such as cardioprotective, neuroprotective and antiobesity properties. Further, it is also reported to have antidiabetic, anticancer and antibacterial effects. Quercetin is reported to have a neuroprotective effect and is scientifically proven by various investigations. It is well established as a therapeutic agent which effectively reduces Aβ aggregation and enhances neurogenesis with inflammatory cytokine inhibition. Quercetin effectively stimulates the nuclear factor erythroid 2-related factor 2- antioxidant response element (Nrf2-ARE) pathways during neurodegenerative diseases and exerts neuroprotective properties. It is also well indicated with improved antioxidant biomarker, superoxide dismutase (SOD) and glutathione (GSH)) enzymes during AD conditions (Sandhir *et al.*, 2015). Quercetin can also improve cholinergic function and enhance the behavioural and habituation memory in rats. Quercetin is nano-formulated into nanoparticles of conjugated super paramagnetic iron oxide and is reported to have enhanced effect when compared to the unformulated plain quercetin. Quercetin-nanoparticle (QT-SPIONs) is a better drug to clinically treat the memory loss and associated neurodegenerative disorders. QT-SPIONs in the preclinical study improved the antioxidant function during AD conditions and improved spatial learning memory (Amanzadeh Jajin *et al.*, 2021). It exhibited AChE inhibitory effect and improved the cholinergic transmission. Treatment with quercetin in animal models very highly enhanced the catalase, glutathione peroxidase and superoxide dismutase. Incorporating quercetin-modified sulphur nanoparticles (Qc@SNPs) in microbubbles (MB) (Qc@SNPs-MB) designed to mediate the momentary opening of BBB and delivery the nanoparticles in conjunction with ultrasonification exhibited improvement in cognitive level in AD mice with reduction in the loss of neuron. In addition, Qc@SNPs demonstrated reversed up-regulation of protein kinase and the C/EBP homologous protein induced by thapsigargin in SH-SY5Y cells, which significantly decreased the apoptosis of the nerve brought on by endoplasmic reticulum (Liu *et al.*, 2020).

3.3 Hesperidin

The two forms of flavonoid hesperidin (Figure 4-glycone flavonoid) and hesperetin (aglycone flavonoid) are commonly found in citrus species.

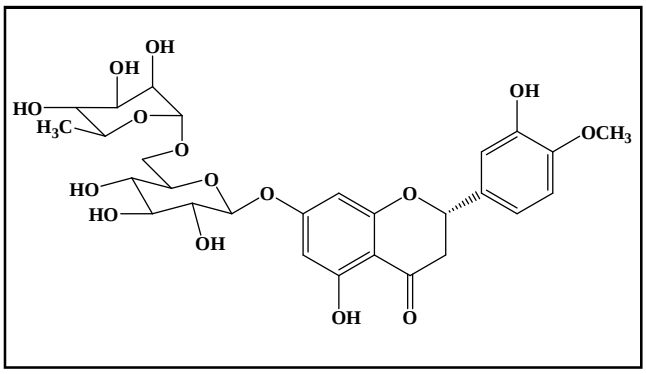

Figure 4: Hesperidin.

Hesperidin and hesperetin were endowed with good antioxidant properties and is therapeutically active in many studies including preclinical and clinical. They are reported to have antioxidant effect, neuroprotective, cardioprotective and anti-inflammatory properties. The gold nanoparticle delivery system is considered one of the suitable systems for targeting drugs in the brain. Gold nanoparticles are also reported to have excellent biocompatibility and have low toxicity profile. Hesperidin was formulated as gold nanoparticles (HSP AuNPs) by chemical reduction method and evaluated in rat model of AD. The characterisation of formulated HSP AuNPs was performed by microscopically and spectroscopically. The memory evaluation was performed on diabetes-induced animal model with AD type as diabetes and loss of memory is one of the common comorbid factors during ageing for susceptible individuals. The rats were induced with alloxan to produce diabetic conditions and treated with two formulations, one with plain hesperidin (50 mg/kg) and another with HSP AuNPs (20 mg/ kg). This study found that the HSP AuNPs treated animals have recovered well with enhanced brain antioxidant enzymes (SOD, catalase and GSH). The memory test performed with behavioural evaluation in the treated rats indicated good memory retention in Y-maze, elevated plus maze and radial arm maze. Histopathological studies on brain tissue affirm the neuroprotective effect of HSP AuNPs (Pradhan *et al.*, 2022). Additionally, research has shown that the HSP nanoparticle can reduce AD-related anxiety by enhancing the brain's antioxidant (Hajizadeh Moghaddam *et al.*, 2020).

3.4 Mimosine

The plants of the subtropical and tropical area of *Mimosa* species contain a component called mimosine [β-[N-(3-hydroxy-4-oxypyridyl)]-α-aminopropionic acid], is similar to tyrosine in structure and non-protein amino acid in nature (Figure 5).

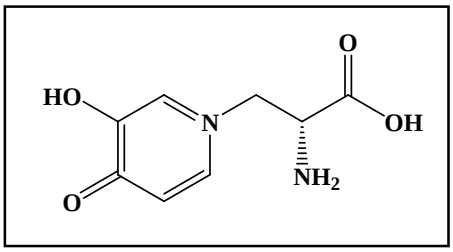

Figure 5: Mimosine.

Mimosine is reported to have various activities, including a cytotoxic profile. The biomolecule mimosine is prepared as functionalised gold nanoparticles (AuNPs) by potassium hydroxide reduction and followed the standard preparation of AuNPs. The prepared AuNPs were characterised by transmission electron microscopy and fluorescence microscopy. The mimosine gold nanoparticles (Mimo-AuNPs) were evaluated using the molecular docking method, and also *in vitro* cell culture tests have been established in mouse cortical neuronal cells. The study revealed that the ability of Mimo-AuNPs to penetrate the BBB is well assured and afforded neuroprotective effects against neuronal cells induced with Aβ toxicity. This indicated the therapeutic potential of Mimo-AuNPs. The Mimo-AuNPs mechanistically interact with the hydrophobic domain of Aβ1-42 due to its aromatic moiety (Anand *et al.*, 2021).

3.5 Naringenin

Citrus fruits including grapes, lemons, and mandarins contain a polyphenolic component called naringenin (Figure 6), which has been linked to a number of therapeutic benefits. Naringenin is an extremely potent antioxidant, having good BBB penetrability and has effects treating several diseases such as diabetes, depression, cardiac disorders, and neurodegenerative disorders.

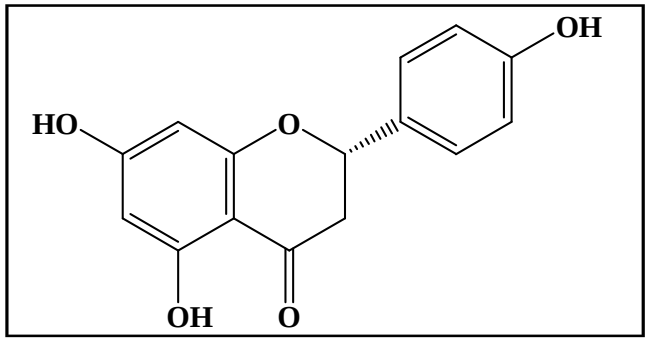

Figure 6: Naringenin.

Previous studies with naringenin (50 and 100 mg dose/ kg) indicated the reversal of scopolamine-induced amnesia by improving the biogenic amines such as serotonin, noradrenaline and dopamine and antioxidant enzymes. It was also prepared into nanoemulsion (NRG-loaded nanoemulsion) and found enhanced bioavailability in conditions with cerebral ischemia. A novel formulation for nasal administration with naringenin (NRG-loaded *in situ* gel) with poloxamer-407/chitosan was formulated. It has thermoresponsive and mucoadhesive properties for nasal administration, having gelling capacity of 28.3^{O}C. It was evaluated with bovine nasal mucosa (*Ex vivo*) permeation and exhibited good delivery of when compared to the normal nanoemulsion prepared with NRG. Intranasal administration in rats indicated the good drug delivery of NRG and improved the locomotor activity of rats. NRG- loaded nanoemulsion also exhibited pre-eminent neuroprotective properties *in vitro* neuronal cell cultures (SH-SY5Y neuronal cells) exposed to Aβ when compared to the free NRG. This concludes the better therapeutic effect of NRG-loaded nanoemulsion (Bhia *et al.*, 2021).

3.6 Luteolin

Luteolin is a tetrahydroxy flavone (Figure 7) distributed in carrots rosemary, olive oil, green pepper, parsley, thyme, broccoli chamomile tea and oregano. It is reported to have antioxidant, anti-inflammatory, neuroprotectant and antidiabetic.

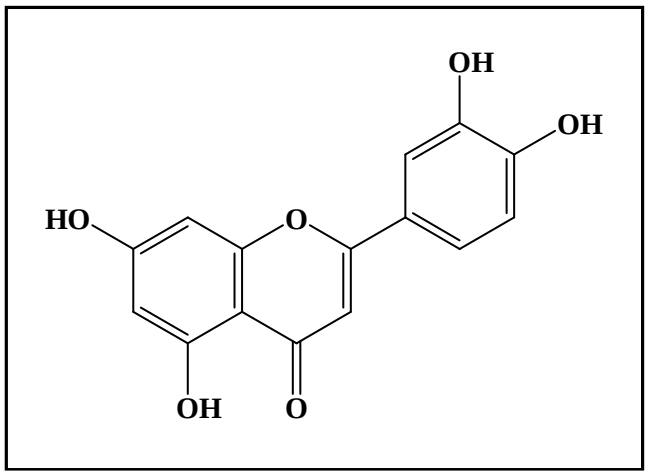

Figure 7: Luteolin.

It is effective against Aβ toxicity in mice and have memory-enhancing effect in mice. Luteolin is developed as a novel formulation as chitosomes using the anionic liposomes method. The chitosan decorated nanoparticles are studied in sporadic Alzheimer's disease (SAD) in the mouse by injecting intracerebroventricular administration of streptozotocin (ICV-STZ-3 mg/kg). The dose selected for the study was 2 mg/kg/day through the intranasal route and administered for 21 days in the ICV-STZ-induced animal. Behavioural assessment such as water maze and y-maze is performed to ensure the learning memory property and is revealed to improve cognition with the treatment of chitosan decorated nanoparticles of luteolin. The antioxidant markers such as SOD, GSH and the antioxidant-responsive elements (NRF2) pathway are improved in the brain. The anti-inflammatory mediators' such NOS, TNF-α COX-2 and NF-KB were controlled by the treatment of luteolin-loaded chitosomes decorated (LUT-CHS). The study also estimated the CERB and found that the treatment improves the response and demonstrates neuronal signalling improvement with LUT-CHS. All over the LUT-CHS reduced, the Aβ aggregation in brain of sporadic AD mouse. This suggested that the nanodrug delivery system with LUT-CHS is neuroprotective and safe with non-invasive drug administration (Abbas *et al.*, 2022).

3.7 Curcumin

A natural polyphenolic compound (Figure 8) obtained from turmeric and possesses innumerable pharmacological properties from anti-inflammatory to anticancer activities.

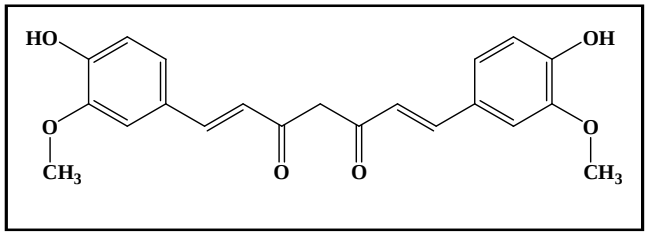

Figure 8: Curcumin.

Various studies have been established by curcumin and has also been in clinical trials for treating AD. Nanoparticle formulations with curcumin is a promising therapeutic agent and is evaluated for various diseases. For AD treatment, curcumin-loaded gold nanoparticles are prepared and evaluated. Lipid core nanocapsules of curcumin (NLC C) is prepared by the nanoprecipitation method. Swiss albino mice injected with Aβ peptide intracerebroventricularly is treated with NLC C (10 mg/ml) for the alternate day until 12 days. Behavioural tests with open field, tail suspension test and forced swimming test were carried out and found to improve with behavioural memory (Fidelis *et al.*, 2019). SOD and catalase levels were improved in the prefrontal cortex region of the brain. Aluminium (Al) is neurotoxic, and its exposure to animals through drinking water can induce AD pathology. Curcumin-loaded solid lipid nanoparticles (C-SLNs) were prepared by the microemulsion method and treated with Al-induced male Lacca mice. The animals were treated in various groups with 50 mg/kg of free curcumin and C- SLN 1, 12.5, 25, 50 mg/kg in various groups for 6 weeks and administered with aluminium chloride (100 mg/kg orally). Water maze behavioural study was performed and found that memory improvement in spatial learning. In biochemical parameters, it was found that the treatment controlled the AChE and improved the antioxidants (GSH, catalase and SOD). Histopathological study revealed that the C- SLN protected the neurons from aluminium-induced toxicity and the nanoparticle formulation exhibited a higher effect than the free curcumin (Kakkar and Kaur, 2011). In another, study magnesium oxide nanoparticles (MgONPs) and solid lipid nanoparticles (SLNs) of curcumin is prepared and evaluated the effect in Al-induced neurotoxicity in albino rats. The acetylcholinesterase and acetylcholine content are estimated after the treatment and found that the nanoformulations have better therapeutic effect by inhibiting AChE and improving the levels of acetylcholine (Ganna *et al.*, 2020). In another study, poly lactic-co-glycolic acid (PLGA) nanoparticles loaded with curcumin (PLGA-NP-Cur) were studied on neuronal differentiation and proliferation, indicating that the bioavailability is improved, which is analysed by transmission electron microscope. Throughtrans mission electron microscopy (TEM) analysis. The drug availability is also driven by neuronal stem cell (NSC) proliferation. In rat model (Aβ induce) of AD, the PLGA-NP-Cur exhibited a neuroprotective effect by improving the hippocampal neurogenesis. The studies with other novel formulations of curcumin in poly lactic-co-glycolic acid-polyethylene glycol (PLGS-PEG) conjugated with B6 peptide (to enhance the optimal bioavailability) was loaded with curcumin (formulation: PLGA-PEG-B6/Cur) and administered it into HT22 cells and also in transgenic mice model (APP/PS1). *In vitro* studies proved that the PLGA-PEG-B6/Cur is biocompatible and non-toxic. In *in vivo* evaluation, the treatment of PLGA-PEG-B6/Cur in transgenic mice (APP/PS1 mice) exhibited the improvement in escape latency in water maze and immunostaining markedly shown the reduction in tau hyperphosphorylation and Aβ aggregation(Fan *et al.*, 2018). Overall, the studies suggest that curcumin nanoparticle formulations offer an alternative and effective treatment for neurodegenerative diseases.

4. Conclusion

In conclusion, it is evident that novel formulations with nanoparticle design have a potential impact on advanced drug delivery systems. The phytonanoparticle in various formulations has most remarkable therapeutic effects by enhanced BBB penetrability and non-toxic. Generally, the phytocompounds were effective antioxidants and possessed neuroprotective effects, especially in AD. Many biomolecules from plants were reported to possess therapeutic effects in preclinical models. However, they have a limitation when designed for clinical uses due to their low bioavailability and penetrability towards the brain. The application of nanomedicines triggered the

avenue for target delivery and enhanced bioavailability of phytocompounds which made benefits and transformed the brain drug targeting for the treatment of Alzheimer's type of neurodegeneration.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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