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Review Article

Current Strategies in Treating Alzheimer and Nano-Based formulation of Curcumin as new Drug Delivery Systems against Alzheimer: A Review of *in-vivo* and *in-vitro* Evidences

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Abstract

Alzheimer's is a neurodegenerative disease that have caused many problems for the global health system.. Today, due to the increase in life expectancy and the age of the population, the number of people diagnosed with Alzheimer›s Disease (AD) is increasing [1]. AD is usually identified by cognitive dysfunction and disruption in behavioral abilities, leading to the decrease in humans productivity and function in daily life [3]. Indeed there is a growing necessity for prevention and treatment of AD [4]. Progression of AD is linked with numerous neuropathological features such as accumulation of Amyloid-β (Aβ) etc. Development of promising treatments for AD have been challenging, with no drugs approved to date. Although in trials some drugs such as Aducanumab was effective in reducing Aβ plaques in the brain, clinical out-comes were not considerable [5-8]. Due to failure of multiple trials on different drugs, many researchers have focused on natural compounds [9-11]. Curcumin as one of the most popular polyphenols, have received interests due to its unique properties in targeting Aβ's aggregation [12,13]. However curcumin has disadvantages such as poor bioavailability and chemical instability [14]. To overcome these disadvantages, Nano-drug delivery systems have shown trusting results such as appropriate targeting, high bioavailability and reducing side effects [15]. In this study we have investigated novel curcumin loaded Nano particles to highlight the advantages and disadvantages of Nanoparticles in delivery of Curcumin in AD.

Keywords: Alzheimer; Curcumin; Nano; Nanoparticle; Drug; Brain

Introduction

What Cause Alzheimer?

Due to researches done on this subject, in common regions with prevalence of Dementia; Alcohol, Physical activity and Diabetes and in the next place other factors such as smoking, social engagement, anxiety, hormones, hyper/hypotension are the main cause of Dementia [16].

Alcohol

Alcohol could affect neurotransmitter in different ways which causes to harmful consequences to these pathways. Ethanol triggers inhibitory γ-aminobutyric acid (GABA) receptors, followed by the stimulation, the excitatory glutamate receptors will be suppressed. Chronic alcohol consumption can change the microbiome and causes the neuroinflammation [17]. External negative life aspects can change gut microbiome. Negative life habits such as poor die t and alcohol consumption are considered as critical risk factors for development of spordiac AD [18,19].

Physical Activity

The brain has high sensitivity to exercise, exercise in rodent models causes the neurogenesis within hippocampal and dentate gyrus's areas, also it will enhance learning and memory abilities [20]. Evidences in this area suggested the beneficial effect of physical activity and exercise intervention on AD [21].

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Diabetes

Diabetes is associated with various problems like nephropathy, neuropathy, retinopathy, diabetic foot, cognitive impairment, and many more. Age-related memory impairment is a complication having its major effect on people suffering from diabetes and Alzheimer's. As compared with normal individuals Patients suffering from diabetes are at two times higher risk of developing cognitive dysfunction [22]. In recent years Many researches have been done on correlation between Diabetes and Alzheimer, Due to the significant correlation between two diseases the term " diabetes type 3 "or "brain diabetes" have been proposed [23]. Today it is confirmed that type 2 diabetes is associated with greater brain atrophy and cognitive decline [24].

Smoking

Among other risk factors, smoking is one of the important ones that is associated with Dementia and also can be related to currency and mortality of AD [25]. Smoking may result in cerebral oxidative stress which causes the production of Amyloid beta (Aβ) or tau protein pathology. In contrast never smokers had 18% lower risk of AD in compare to continuous smokers which confirms the destructive effect of smoking on cognitive decline [26].

Social Engagement

Life style intervention including social engagement has considerable effect on AD and Cognitive abilities [27]. Low social engagement may be a marker of neurocognitive vulnerability in older adults who are cognitively normal but have evidence of AD pathophysiologic change [28]. Dyer et al. [29] in a research have suggested that in patients with AD it is important to maintain the social network. in contrast poor social network in associated with experiencing serious negative symptoms.

Anxiety

AD can result into neuropsychiatric symptoms. Among AD patients, the prevalence of anxiety is about 40% and it can be a prelude of AD. Anxiety can be seen in patients with mild cognitive impairment, mild dementia, or early-onset forms of the disease and may result to clinical syndrome of Alzheimer's disease [30]. It is reported that anxiety convey the risk of AD up to 53%. A meta-analysis done by Santebarbara et al. [31] it has been confirmed that anxiety increases the risk of AD.

Hormone

There is noticeable fact that Alzheimer's and dementia's prevalence are considerably different between sexes. The rate and incidence of AD is notably higher in females. Due to the findings, researchers have now begun to search about the role of sex-dependent hormones in the pathogenesis and cause of the AD [32]. Sex hormones such as estrogen changes rapidly during the female lifespan, these hormones are high during the reproductive years and it will decline naturally during the transition to menopause. Estrogen production during Women life span may increase the risk of AD [33]. Also by the research done by Quinalan et al. [34] it have been confirmed that Thyroid hormones were moderately changed in mild AD dementia with increased serum FT4, and a also there is a decrease in peripheral conversion of T4 to T3 which confirms the reduction of T3. Brain structures involved in AD development was correlated to Serum T3 levels.

Hypertension/Hypotension

Hypertension decreases the structural and functional integrity of the cerebral microcirculation and also causes microvascular rarefaction, cerebromicrovascular endothelial dysfunction and neurovascular uncoupling, which disrupts cerebral blood supply, as a conclusion hypertension considerably increases the risk of both vascular cognitive impairment and Alzheimer's disease [35]. Among the different types of hypotension, it has been reported that the Orthostatic hypotension is common in patients with AD [36]. It is also reported that the prevalence of Orthostatic hypotension was more significant with progression of AD [37].

Amyloid Beta, Tau Protein, Mitochondrial Dysfunction, Dysregulation of Calcium Homeostasis, Proliferation of Microglia

Amyloid Beta

Aβ plaques are made in neuronal endosomes by process of hydrolysis of amyloid precursor protein and this operation is done by two main enzymes: β-secretase and γ-secretase. Under normal condition Aβ has two responsibilities: profusion of activation of synapses and also reducing the synaptic excitotoxicity [38]. But under pathological condition mostly two Aβ, Aβ40 and Aβ42 are produced by abnormal processing of β- and γ-secretase what makes the accumulation of Aβ plaques, is imbalancement of the pathway clearance and production. These small 4 kDa peptides (A4) that are mainly contained of 38 and 43 amino acids, fold into a beta-pleated sheet structures that are highly fibrillogenic. Aβ42 is the most fibrillogenic and the greatest component of amyloid plaques in AD [39].

Tau Protein

Tau belongs to the family of microtubule-associated proteins MAPs that can emerge in brain cells. Alternative splicing of the human microtubule-associated protein gene MAPT leads to six tau isoforms which are contained of 352 to 451 amino acids. A normal tau isoform ratio is necessary for maintaining brain cell homeostasis and preventing neurodegenerative diseases [40]. Tau extracted from healthy adult brains is moderately phosphorylated but in contrast, detergent-insoluble *NFT Tau* isolated from AD brain, is unusually and highly phosphorylated [41].

Mitochondrial Dysfunction

The mitochondrion is a cellular organelle with a special structure that is formed by two membrane that is called: outer mitochondrial membrane and inner mitochondrial membrane. Inner membrane surrounds the matrix. Mitochondria is known as powerhouse of cell and contain its own DNA. During recent decades researches have suggest new hypothesis for explaining AD pathology [42].

Mitochondrial cascade hypothesis stated that mitochondrial function may affect the accumulation of Aβ. Also Reactive Oxygen Species (ROS) is responsible for most of the oxidative stress in body. There are evidences that confirms Due to mitochondrial Damage in AD, the production of ROS increases. ROS is responsible for most of the oxidative stress in body [43].

Dysregulation of Calcium Homeostasis

One of the major secondary messengers is Calcium ion which is involved in cell survival, proliferation, differentiation, transcription and apoptosis. In AD, G protein coupled receptors generate secondary messengers which regulate calcium ho-

meostasis inside cell. But in AD and pathological condition the homeostasis get damaged [44]. In normal condition, During neurotransmission, an increase in intracellular's calcium, following membrane depolarization, transmits the signal to synapses. Therefor calcium signaling is important for neurotransmission, maintaining the synaptic plasticity and generating long term potentiation which is the basis of learning and memory [45].

Proliferation of Microglia

Microglia are the major phagocytic cells in the Central Nervous System (CNS). These cells develop from yolk sac progenitors, migrate into the developing brain, and generate a population of brain-resident phagocytes that persist for life through self-renewal [46]. Microglia cells have different responsibilities in brain as clearing apoptotic cells, releasing growth factors and nurturing neuronal metabolism and development in neurodegenerative diseases, microglia restrain extracellular protein aggregates and clear damaged neurons [47]. Still in pathological condition of AD, at first microglia was thought to be triggered by amyloid deposit. But in recent studies majority of AD risk loci are found near or in genes that in microglia are highly expressed which rises the theory of alteration in microglia 's genes may lead to AD [48].

Current Strategies in Treatment of Alzheimer's Disease

As it was mentioned, AD is one of the most common neurodegenerative diseases. Despite increasing number of Alzheimer cases, there is still no effective treatment to cure or slow down the progression of the disease. Until now only six drugs have been approved by the US Food and Drug Administration (FDA): Aducanumab, Donepezil, Galantamine, Rivastigmine, Memantine, and a manufactured combination of Memantine and Donepezil. the main limitations of current AD treatment are low blood–brain barrier permeability, severe off-target of drugs, and immune abnormality [49,50].

Aducanumab

Aducanumab is a fully human IgG1 monoclonal antibody with a high affinity that acts by breaking down these *β*-amyloid aggregates into smaller oligopeptides or amino acids. Aducanumab has been shown to selectively bind to parenchymal amyloid over vascular amyloid. The medicine at a high dose has the potential to slow down the cognitive decline linked with Alzheimer's in patients with early-onset disease. However, aducanumab does not reverse memory loss [51]. Also aducanumab did not show positive effect on AD patients in comparison to placebo in control trials. The reports have shown that patients treated with Aducanumab have had several side effects such as headache, falls and diarrhea [52,53]. To conclude based on researches in this area, aducanumab can slow down a few symptoms of AD but until now there is no trusted research that shows the strong efficiency of Aducanumab on AD patients.

Donepezil

Donepezil is used to treat symptomatically AD. This drug specifically inhibits the enzyme Acetylcholinesterase (AChE). The main physiological function of AChE is to hydrolyze the neurotransmitter acetylcholine [54]. Unfortunately, due to the presence of Blood Brain Barrier (BBB), donepezil makes severe side effects after continuous administration at a high dose of 5 mg/day, such as diarrhea, bradycardia, vomiting, insomnia and anorexia. BBB in Alzheimer patients is more hindrance which makes the drug delivery to this area even more difficult [55]. Based on researches done on Donepezil, the medicine can improve the cognitive function to a certain degree. However, there is no evidence of significantly delaying the progression of the disease, and it can easily cause side effects on patients [56,57].

Galantamine

Galantamine is an alkaloid phytochemical which can inhibit the AChE activity. the advance feature of Galantamine in this field is the ability of Galantamine in crossing the blood brain barrier. galantamine can significantly reduces mortality and cognitive decline and also improved daily routine activity in mild cognitive decline patients [58]. But it is not clinically proven that galantamine can have disease modifying effect in humans. Also, galantamine does not have the ability to strongly break the vicious circle of Aβ accumulation. It is suggested that early usage of galantamine has efficiency in prevention of AD but there is a strong doubt that Galantamine can be useful in treatment of AD patients [59].

Rivastigmine

Rivastigmine is one of the approved agent for the management of dementia of mild to moderate Alzheimer's disease. this medicine is the only cholinesterase inhibitor which inhibits both AChE and butyrylcholinesterase enzymes in the brain [60,61]. This molecule also has a short half-life and a hydrophilic nature, which makes it difficult for the medicine to pass through the Blood Brain Barrier (BBB) and Cerebrospinal Fluid (CSF) which results to low bioavailability of the drug [62]. Oral consumption of Rivastigmine shows different adverse effects such as nausea, vomiting, diarrhea, and cholinomimetic effects. Also, it have been reported that large plasma fluctuation happens after oral administration which is the main reason for higher incidence of cholinergic side effects [63].

Memantine

Memantine is an oral drug which functions as a noncompetitive N-methyl-D-aspartate receptor antagonist and is approved for treatment of moderate to sever AD. Unfotunatly, studies on mold to moderate and sever AD have shown that memantine has a mild but not considerable effect on clinical symptoms [64,65].

Combination of Memantine and Donepezil

In a network meta-analysis done by Gou et al [66]. it is suggested that combination of both memantine and donepezil is effective on cognitive and neuropsychiatric symptoms but in comparison to memantine alone or placebo is less acceptable [67].

Although today, main treatment strategy of Alzheimer is prescribing approved FDA drugs, many studies are focusing on plant based compounds as they have shown less side effect, and in some cases more efficiency in *in vitro* and *in vivo* studies [68].

Polyphenols Effect on Alzheimer Disease

Polyphenols are plant compound derivation with antioxidant properties. Studies on animals have proved that polyphenols could impact accumulation and reduction of oxidative stress in patients with AD [69]. Fruits, Vegetables, beverages (tea,wine,juices), plants and some herbs have plenty of antioxidants polyphenols [70]. Veriety of mechanisms, such as free

radical scavenging, metal chelation and the modulation of enzyme activities may explain the positive effect of polyphenols on brain [71]. Curcumin is one of the most famous polyphenols which could be one of the potential pharmaceutical agent for protecting brain function [72].

Curcumin and Its Therapeutic Effect

Curcumin a yellow- orange pigment belongs to a chemical class of polyphenols; it is known as diferuloylmethane with a chemical formula of $C_{21}H_{20}O_6$ and a molecular weight of 368.38. Curcumin has several biological activities which is due to its special chemical structure [73,74]. There are three chemical group in Curcumin molecule: two aromatic ring systems containing *o*-methoxy phenolic groups linked by a seven-carbon spacer consisting of an α,β-unsaturated β-diketone moiety. The diketo group shows the tautomerism between two form of keto and enol. This feature indicates Curcumin could exist in equilibrium between the keto and the enol tautomer [75]. Curcumin is derived from a plant named Tumeric (*Curcuma longa*). Tumeric is an aromatic plant from the ginger family (Zingiberaceae). It can usually be found in Iran, Malaysia, India, China, Polynesia and Thailand. Curcumin isolated from turmeric two centuries ago. This polyphenol has been studied in numerous researches on natural compounds and have shown wide therapeutic potential in *in vitro* studies [76]. The compound belongs to a group of plant derivations named Flavnoids. Flavnoid among the medical herbs are a huge subgroup of the family of polyphenolic compounds that are result of secondary metabolism in plants. Various researches in recent years has shown that flavonoids could be effective in prevention and control of common diseases such as cancer, cardiovascular diseases, Alzheimer's, stroke, diabetes, Osteoporosis and rheumatoid arthritis [77]. It is proven that curcumin as one of the most famous flavonoids has beneficial effect on neurological diseases such as AD and it can alter and decrease the disaggregation of amyloid-β plaques, weaken the hyperphosphorylation of tau and provoke the clearance of tau protein [78]. Although curcumin can change the pathological factors of AD's initiation and progression, it has some limitations such as low stability and low bioavailability which can weaken the positive effect of the compound on cells [79]. Also another blockage for curcumin delivery is blood–brain barrier. BBB is the major hindrance for the delivery of curcumin into the brain, resulting into decreasing its therapeutic effects [80]. One of the main solutions to overcome the Weaknesses of curcumin as a therapeutic agent is nanotechnology. Some of the major disadvantages of curcumin-based medication delivery has been alleviated by Curcumin nano formulation [81]. Today numerous studies on Alzheimer are focusing on designing the nano formulation with the most beneficial effect on brain health. Due to the hydrophobicity and low bioavailability of curcumin, encapsulated formations such as liposomes, micelles, cyclodextrin, solid lipid and polymeric NPs could increase sole curcumin's biodistribution and bioavailability [82-84] (Figure 1).

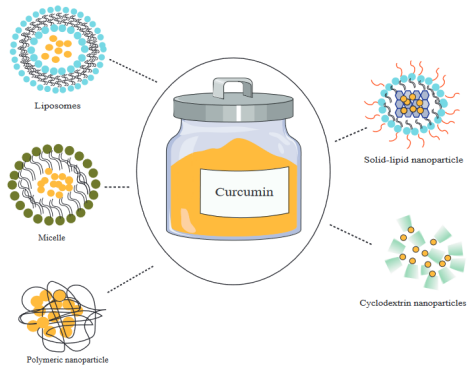

Figure 1: Five different types of important nanocarriers for delivering Curcumin in Alzheimer disease.

Curcumin-Liposome Nano Particles

Lipososmes are structured of lipid components with two parts: hydrophobic head and hydrophilic tail. Liposomes differ from their size, shape and also the number of lipid bilayers. They may have single bilayer (unilamellar), a few bilayers (oligolamellar), or multiple bilayers (multilamellar). We can also modify the rigidity, fluidity and surface charge of the liposomes which makes them a good candidate for delivering drugs in different environment [85]. Lipid nanoparticles, especially liposomes and lipid/nucleic acid complexed nanoparticles are promising formulations due to their stable drug loading, reducing side effects, enhancing efficiency in targeting and also their ability to pass the BBB or plasma membrane barriers. According to these features, liposomes are effective formulations for current untreatable illnesses [86]. In a study done by Chen et al. [87] Curcumin loaded liposome with different kind of Sialic acid coupled formulation, shows high permeation rate crossing BBB. Also Schmitt et al. [88] in a *in vitro* study, experimented the effect and efficacy of Curcumin loaded liposomes in specific brain cells in human. The results have should that the formulation reduces the reactivity of human microglia and actrocytes and also in *in vivo* study, the designed complex could preserve the tissue integrity in organotypic cortex slices in mice.

Curcumin-Micelle Nano Particles

Micelle NPs are usually formed by self assembly of block of copolymers. These type of drug delivery is usually used for encapsulating highly hydrophobic drugs and improving their solubility. Block co polymers can self assemble in solution and make micelles with different size range [89]. Moreover Micelle NPs could improve provide passive and acrive targeting and reducing the side effects of loaded drug on normal cells [90]. Hagl S et al. [91] in a *in-vivo* and *in-vitro* study have found that Curcumin-micelle formulation could improve the Curcumin bioavailability in plasma 1- to 40 times more compare to sole Curcumin. Also in this study it have been proved that curcumin micelles are promising formulation for prevention of mitochondrial damage in Neurodegenerative diseases and brain aging. In another research Preshita P et al. [92] designed Curcumin- cocrystal micelles in aim of enhancing the therapeutic efficiency of Curcumin in brain. The results have shown that Curcumin-cocrystal micelle have high brain distribution and also improves bioavailability, brain uptake, retention and moreover could delay clearance in brain.

Curcumin- Cyclodextrin Nano Particles

Cyclodextrins are cyclic oligosaccharides which are obtained from enzymatic process on stratch. There are three form of cyclodextrin α-, β- and γ- cyclodextrins containing 6, 7 and 8 glucopyranose units. Cyclodextrin is widely used in pharmaceutical application due to their low toxicity. Also Cyclodextrins increases the solubility of hydrophobic drugs in water [93]. Zhan et al. [94] in a research encapsulated curcumin in hydroxypropyl-β-cyclodextrin (CUR/HP- β-CD). The in vitro experiment showed that CUR/HP- β-CD has higher cellular uptake in compare with CUR-encapsulated chitosan-coated poly (lactic-co-glycolic acid) nanoparticles. Also CUR/HP- β-CD reduces cellular cytotoxicity and decreases inflammation markers such as TNF- α and IL-6. In a study done by Quitschke et al. [95] cyclodextrin solubilized

Table 1: Nanoparticle-curcumin formulation effect on AD related biomarkers and cell line; in-vivo and in-vitro studies.

NPs Type	Study Type	Author	Effect On
Curcumin loaded liposome coupled with Sialic acid	*In vivo* study on mice	Chen et al. (87)	High permeation rate Through blood-brain barrier
Curcumin loaded Liposomes	*In vitro* study on microglia and astrocyte of human cell culture / *In vivo* study on murine acute brain slices	Schmitt et al. (88)	Reduction in glial scarring associated microglia and astrocyte reactions
Curcumin micelles	*In vitro* study on mitochondrial function in PC12 cell line/ *In vivo* study on NMRI mice / *ex vivo* in isolated mouse brain mitochondria	Hagl S et al. (91)	In isolated mouse brain, Curcumin micelles are efficient in mitochondrial swelling. Curcumin micelles are more efficient in protecting PC12 cells from nitrosative stress.
Curcumin- cocrystal micelles	*In vitro* cytotoxicity study on U87MG cell line/ *In vivo* pharmacokinetic and biodistribution studies in rodent model	Preshita P et al. (92)	Curcumin-cocrystal micelle have high brain distribution and also improves bioavailability, brain uptake, retention and it would delay clearance of curcumin in brain.
Encapsulated curcumin in hydroxypropyl- β-cyclodextrin	*In vitro* study on BV-2 and SH-SY5Y cell line / *In vivo* study on mice models	Zhan et al. (94)	Encapsulated curcumin in hydroxypropyl- β-cyclodextrin, decreases TNF-α and IL-6 levels. And also the complex showed high bioavailability and brain distribution
Cyclodextrin-solubilized curcuminoids	*In vitro* study on NT2/D1 cells/ *in vivo* study on female APP_{SWE}, PS1dE9 transgenic mice	Quitschke et al. (95)	Curcuminoids solubilized in 10% HP-γ-CD in NT2/D1 cells shows less binding compare to curcuminoids in solubilized in mouse serum/ intravenous injection of cyclodextrin-solubilized curcuminoids, reduces the plaque load to approximately 70% of the control value
β-cyclodextrin-curcumin conjugates	*In vitro* study on Primary cultures of cortical neurons from rat fetuses/ *In vivo* study on rat embryonic cortical neurons	Ben mihoub et al. (96)	Water solubility of Curcumin- β-Cyclodextrin in nanoconjugates were evaluated compare to sole curcumin also the complex reduces cell toxicity of curcumin
Curcumin-loaded solid lipid nanoparticle	*In vivo* study on Wild Type and in TgCRND8 mice models	Campisi et al. (100)	The expression levels of Bcl-2, Cyclin-D_1, and caspase-3 cleavage was evaluated after administering curcumin-solid lipid nanoparticle to animal models. Also the complex modulates the TG2 isoforms which repairs cellular damage in AD mice models. Thus significant improvement of cognitive performance and memory function was observed in TgCRND8 mice models
Curcumin encapsulated in solid-lipid-nanoparticle	*In vitro* study on neuron cells from hippocampus/ *In vivo* study on Pregnant mice and C57BL/6 mice	R Huang et al. (101)	Curcumin-solid lipid nanoparticle reduced neuronal apoptosis through Bcl2 family and P38 MAPK pathways compare to sole Curcumin through *in vitro* and *in vivo* study
Curcumin-loaded PLGA-PEG nanoparticles	*In vivo* study on brain injured neonatal rats	Pontes-Quero et al. (108)	The curcumin- loaded nanoparticles were able to overcome the impaired blood–brain barrier, diffuse effectively through the brain parenchyma, localize in regions of injury, and deliver a protective effect in the injured neonatal brain

curcuminoids was injected to mice and after 11 and 12 months, the plaque concentration is reduced up to 70% in compare with control value. Ben mihoub et al. [96] in a study synthetized Cur-β-Cyclodextrin nanoconjugates to improve the solubility and reduce cell toxicity of Cur. At last the finding revealed that the nano formulation has better water solubility and in vitro biocompatibility in compare with sole Cur. The results indicated that Cur- β-Cyclodextrin nanoconjugates could have positive effect in prevention of neurodegenerative diseases.

Curcumin-Solid Nanoparticles Complex

Solid Lipid Nanoparticle (SLNs) commonly have spherical shape with a diameter in the range of 50 to 1000 nm. The most important parts of SLN formulations include lipids, which in the room temprature are at solid state, emulsifiers and sometimes a mixture of both, active pharmaceutical ingredients and an adequate solvent system [97]. SLNs can hold both hydrophilic and hydrophobic drugs. They can be made up of biocompatible ingredients and due to these features, SLNs are one of the most considered choices for drug delivery. SLN's surface modification may provide unique features to them such as mucoadhesiveness and targeting capability [98]. Gupta et al. [99] in a research for controlling the oral bioavailability of curcumin had fabricated a curcumin loaded with solid nanolipid particle by using tristearin and polyethylene glycol (PEG)ylated emulsifiers, the results suggested that bioavailability of curcumin can be improved by altering interfacial properties of SLNs which can be used in functional foods and pharmaceuticals. Also Campisi et al. [100] in a experiment done on Alzheimer mice models, have observed that the curcumin loaded solid nanoparticles can trigger the apoptotic pathway or modulate the ability of protein in repairing cellular damage in brain. R Huang et al. [101] in a study had capsulated curcumin in solid lipid nanoparticle for better neuroprotective efficacy. In vitro experiment proved that Cur-SLNs by significantly decreasing the level of free radical and reversing mitochondrial activity, functioned much better against neuronal apoptosis than sole Cur. To conclude curcumin loaded solid nanoparticles can be much more effective in Alzheimer's disease than curcumin by itself. The efficiency is mostly due to increased bioavailability features of curcumin when is loaded with solid nanoparticles.

Curcumin-Polymeric Nanoparticle Complex

Polymeric nanoparticles are blocks of co-polymers with natural and synthetic sources such as albumin and polysaccharides [102]. These particles have the size range between 1 to 1000 nm and can make complex with active compounds. Nanoparticles are divided into two groups: nanocapsules and nanospheres. These two polymeric subgroups are mainly different by their morphological shape [103]. NPs as drug carrier has various advantages such as strong bioavailability, improving the drug therapeutic index, controlled release and the ability to protect the drug from unwanted interaction with environment [104,105]. There are several researches that have showed the therapeutic effect of Polymeric NPs in combined with antitumor drugs. Polymeric NPs would enhance antitumor efficiency, in-

hibiting metastases and also reduce the side effects [106]. In a research done by Pontes-Quero et al. [107] Curcumin loaded on polymeric nanoparticles shows good encapsulation efficiency and good curcumin release profile. Also, curcumin loaded on polymeric nanoparticle were not cytotoxic in different range of concentration and were effective in reducing inflammatory markers. Joseph et Al. [108] in a research have loaded curcumin into poly(lactic-co-glycolic acid)-poly(ethylene glycol) particles to examine the effectiveness of drug delivery to the brain. The examiners have concluded that CUR-polymeric NPs had overcome the BBB and also the complex has passed through parenchyme in brain.

Conclusion and Perspective

In last decades, AD patients have been increasing due to change in lifestyle. Numerous medical and psychological factors may cause AD, such as lack of physical activity, Consuming alcohol, Diabetes, smoking loneliness etc. There is no proved evidence that what may cause AD but there are several theories that indicates the pathological cause of AD including accumulation of Aβ plaques, tau proteins, mitochondrial dysfunction, Dysregulation of Calcium homeostasis and Proliferation of microglia. Due to difficulties of drug delivering into the brain aria in AD, such as existence of BBB and rapid clearance of molecules in this area, until now treatment of AD has been challenging for medical system and scientists. Today nano based biomaterials have drawn attention for efficient drug delivery in brain. Most NPs have unique physical and chemical properties which make them a great candidate for safe deliver of drugs. Many NPs have the ability to cross BBB due to their small size or interaction with endothelial cells in BBB. Moreover, today there are few drugs which have been approved by medical system such as Aducanumab and Donepezil etc. But there are a lot of doubts about their efficiency in crossing BBB, also they would cause numerous side effects in patients with low positive effect on delaying the symptoms. Today it has been proved that plant-based compounds such as polyphenols have antioxidant and anti inflammatory effects in brain. Cur is one of the potent polyphenols with strong properties in reducing brain inflammatory with least side effects compare to approved drugs. However, Cur molecules are hydrophobic which makes it hard for them to cross cells. Also, Cur molecules have low stability and low bioavailability which decreases effectiveness of Cur in treatment of AD. Loading Cur on NPs would make Cur to overcome negative features in crossing BBB and in addition, adding NPs to the complex, improves stability and bioavailability of Cur. In this review different NPs-Cur formulations for treatment of AD which have been designed in recent related articles have been mentioned and discussed.

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