NANO HERBAL FORMULATION: AN IMPACTFUL APPROACH FOR ALZHEIMER DISEASE

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Abstract

Alzheimer's disease (AD) is a neurobiological disorder that impairs motor and cognitive function. Currently available drugs like acetylcholinesterase inhibitors fail to prove their efficacy due to poor brain permeability, lower solubility, and slow bioavailability. Blood brain barrier and enzymatic degradation are major challenges for the treatment of AD. Herbal drugs and phytoconstituents have proven their efficacy in the treatment of this disease. Phytoconstituents also have poor availability across BBB as well as less systemic bioavailability which are major obstacles for their use but since this approach reduces systemic toxicity thus these medicines are more researched and promoted for treatment of neurological diseases like AD.

Nanotechnology improves BBB permeability and bioavailability of drug. This technology can be used to improve bioavailability as well as BBB penetrability of phytoconstituents used for the treatment of AD. Nanocarriers have variable and interesting features that can be used with plant based medicines for the treatment of AD.This review summarizes the impact of nanotechnology on the development and improvement of efficacy of phytoconstituents for effective treatment of AD.

Keywords: Alzheimer disease, Phytoconstituents, Nanotechnology, Blood-brain barrier, drug permeability, acetylcholinesterase inhibitors.

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DOI: 10.48047/ecb/2023.12.si10.00322

1. INTRODUCTION

Neurodegenerative disease is characterized by the gradual loss of neural function. It refers to a group of conditions that involve extrapyramidal movement, as well as cognitive and behavioural difficulties. Which appear for no apparent reason and continue to progress. Proteotoxic stress and its attendant anomalies in the ubiquitin –proteasomal and autophagosomal/lysosomal systems, oxidative stress, programmed cell death, and neuroinflammation are all associated with increased neuronal impairment and mortality in neurodegenerative disorders [1]. Age is a major risk factor for neurodegeneration[2]. Alzheimer's disease (AD) and Parkinson's disease (PD) are major neurodegenerative illnesses that primarily affect the elderly, and the risk of developing the disease increases with age[3].

The most prevalent cause of dementia is Alzheimer's disease (AD). Age, family history, head trauma, hyperlipidemia, depression, diabetes mellitus, and vascular variables are all substantial risk factors [4]. The early signs of dementia are frequent memory loss and poor judgement. The patient's symptoms, as well as those of those who care for him, become more severe as the condition develops. The patient is entirely degenerative at this point and requires continuous monitoring[5]. Intracellular neurofibrillary tangles (NFTs) and extracellular amyloid beta plaques are linked to Alzheimer's disease [6]. According to the "2021 Alzheimer's disease facts and figures" report, the mortality rate owing to Alzheimer's disease has climbed to 145.2 percent in the United States between 2000 and 2019. They also supplied data on predicted risk in males of 10.5 percent at 45 years old, 11.6 percent at 65 years old, and females of 19.5 percent at 45 years old, 21.1 percent at 65 years old [7].

Only cholinesterase inhibitors, such as donepezil, galantamine, and rivastigmine, and NMDA receptor antagonists, such as Memantine, have been approved by the US Food and Drug Administration (FDA) for symptomatic treatment of AD.[8] Acetylcholinesterase (AChE) appears to be a highly effective therapy target for the onset of symptoms in Alzheimer's disease (AD) caused by cholinergic depletion, a consistent and early finding in AD [9] [10]. The amount of acetylcholine (ACh) in the cholinergic synapse is directly increased by cholinesterase inhibitors. There has been some improvement in cognitive performance in Alzheimer's patients [11]. Memantine has been found to inhibit neuronal death caused by excitotoxicity [12]. In randomised clinical trials of these medicines, however, substantial dropout rates and severe adverse events have been documented. As a result, safety concerns about cholinesterase inhibitors and memantine have been raised [13]. High-dose requirements, inadequate bioavailability, quick first-pass metabolism, and poor pharmacokinetics are some of the drawbacks of drug delivery tablets, capsules, and liquids [14].

Herbal methods for Alzheimer's disease have gained popularity due to the side effects, inefficiency, and contraindications of conventional drugs. Ayurvedic treatments tend to increase ACh levels or decrease AChE levels in the brain, which can aid in the treatment of Alzheimer's disease. Salvia officinalis, which inhibits cholinesterase, and Panax notoginseng, which is claimed to improve memory and learning ability [15], are two examples of therapeutic plants. Other medications have been examined, such as selegiline, oestrogen, Vitamin E, and anti-inflammatory pharmaceuticals, although their usage is still contentious [16]. Herbal techniques, on the other hand, have drawbacks. They are unable to pass the blood-brain barrier (BBB). The development of medicinal medicines from natural products faces significant hurdles, including obtaining large quantities of active compounds[17]. These medications are commonly linked to negative side effects and do not treat the disease by altering its pathophysiology [6].

Nanoparticles can circumvent these obstacles by increasing permeability across the blood-brain barrier and delivering optimum efficacy at a lower dose. These systems can be utilised to distribute medications to specific cells or tissues, increase bioavailability, maintain drug release, or solubilize pharmaceuticals for systemic distribution [18]. When a drug is loaded into an appropriately constructed nanocarrier and crosses the BBB and accumulates in the relevant neuronal cell, it can boost drug concentrations in brain cells compared to the drug alone [19]. Organic (liposomes, polymers, solid-lipid NPs, emulsions, and dendrimers) and inorganic (silica, carbon, and gold) nanodelivery systems can be generally categorised based on the nature of the carrier material [14]. In this review, we looked at Alzheimer's risk factors, treatment obstacles, and nanotechnology techniques using phytoconstituents to solve such challenges.

Risk Factors

Age

Aging is the most prevalent cause of Alzheimer's disease. It has been discovered that at the age of 65, there are more incidences of disease onset that progresses. Younger people are more likely to develop the disease [20]. There is an age-related

decline in brain weight and volume, enlargement of ventricles, and loss of synapses and dendrites in specific areas accompanied by SP and NFT in a cognitively intact brain [21]. Changes in cortical neurotransmitters are difficult to understand, just as they are in normal ageing [22]. Early pathological changes in AD patients are difficult to identify from those in a healthy elderly person [23].

Diet

Several micronutrients, such as antioxidants, lipids, vitamins, and carbs, can help to lower the risk of Alzheimer's disease. Although the effects of these nutrients on AD are unclear, they are thought to play a role in the progression of AD by reducing oxidative stress and amyloid beta-peptide (A) formation. Vitamin A and -carotene are nutrients that inhibit the development of A oligomers and fibrils [24]. However, some saturated fatty acids and a high-calorie diet have been linked to an increased risk of Alzheimer's disease[25]. Malnutrition is considered a risk factor for Alzheimer's disease. Folate, vitamin B12, and vitamin D deficiency have all been linked to a decline in cognitive function[26]. Patients with Alzheimer's disease also have issues with eating and swallowing, which might raise the risk of malnutrition[27].

Medical factors

Cardiovascular disease: Hypertension is considered as a major risk for stroke. There has been reliable clinical data on the prevalence of poststroke dementia, increasing the risk of AD in elderly [28]. It has been seen that stroke could promote the production of Aβ, interfere with Aβ clearance, and/or aggravate synaptic and neuronal loss already triggered by Aβ and tau pathology[29] Heart failure may cause cerebral hypoperfusion and changes including white matter hyperintensity (WMH). A study suggests that reduced cerebral perfusion is related to greater Wmh, which causes cognitive impairment [30].

Atherosclerosis can also be considered as a risk factor for AD. Cholesterol is consistently associated with AD. High levels of cholesterol can be linked to increased levels of Aβ and greater cognitive impairment leading to progression in AD. Cholesterol seemed to have impaired Aβ degradation and promoted its production [31]

Obesity: Chronic inflammation, oxidative stress, as well as mitochondrial dysfunction are all factors that contribute to neurodegenerative diseases[32]. Increases in BMI in middle age are connected with an increased chance of developing Alzheimer's disease (AD).[21]

Type-2-diabetes: according to the study, there are several factors that link diabetes to AD, including oxidative stress, formation of advanced glycation end-products (AGEs), and overt immune system activation. These factors represent common targets for both the diseases[33].

Smoking

In a study conducted, it was found that smoking was associated with faster declines in verbal memory and with slower speeds of visual search[34]. Another study reported smoking increased the severity of some abnormalities typical of AD, which includes amyloidogenesis, neuroinflammation, and tau phosphorylation. This suggests that cigarette smoking may increase the onset and exacerbate the features of AD [35].

2. Challenges of brain drug delivery

Drugs that affect the Central Nervous System (CNS) must be delivered to the brain (CNS). Most medications cannot cross the blood-brain barrier (BBB) and enter the brain. As a result, most medication molecules are too big to penetrate the blood-brain barrier (BBB). Despite the fact that tiny pharmacological molecules are considered capable of crossing the BBB, nearly 98 percent of the compounds tested did not[36]. Tight connections between endothelial cells impede paracellular mobility. Lipophilic medicine with a molecular weight of less than 600 da, on the other hand, can pass through endothelial cells [37]. The combination of high lipophilicity and low molecular weight is required for efficient drug penetration. Due to its 800 Da molecular weight, Vincristine has a high lipid solubility, however its ability to traverse the BBB is limited (Grieg et al., 1990). Even though small-molecule peptide-mimetic drugs have been found to be effective, their dicarboxylic moiety prevents them from crossing the BBB (Ohlstein et al., 1994). As a result, to demonstrate its pharmacological activity, this medication may require conjugation to a BBB drug targeting system for penetration.

Its not just a physical barrier that stands in the way of these medications' development. Drugs and other exogenous compounds may be prevented from entering the brain by the presence of a number of enzymes found in the blood-brain barrier that are known to break down these substances in the liver. [38]. The biotransformation (functionalization/conjugation) of the drug is carried out by multigene families of isoenzymes. Numerous neurotransmitter-metabolizing enzymes are expressed in the BBB, including monoamine oxidases (MAO), catechol O-methyl transferase (COMT), cholinesterase, GABA

transaminase, aminopeptidases, and endopeptidases [39] [40]. Phase 1 and phase 2 enzymes are responsible for different parts of the drug metabolism process. cytochrome P450, UDP-glucuronyltransferases (UDPs), glutathione S-transferases (GSTs), sulphotransferases (SULTs), and N-acetyltransferases (NATs), particularly NAT2 in phase 2 according to the percentage of drug metabolised by them. Some analgesics, such as diclofenac and phenacetin, are metabolised by CYP46A1[41]. CYP2E1 metabolises anaesthetics and ethanol [42]. In addition to antidepressants and antipsychotics, CYP2D6 metabolises a number of other CNS medications. Reactive epoxide is inactivated by membrane-bound epoxide hydrolase, which is found in isolated microvessels[38]. Figure 1 depicts various methods of delivering drugs to the brain over the BBB, as shown in the figure.

3. Role of herbal nanoherbal formulation

Nanomedicine is a new concept developed by the convergence of nanotechnology and medicine. They are more safer, effective and have lower healthcare cost [43]. Recently, the attention has shifted towards a novel drug delivery system using herbal drugs [44]. Due to the side effects of current therapies, the attention has laid over the herbal approaches for the treatment of AD and other diseases [45]. They are preferred over the synthetic due to their negligible harmful and deleterious effects [46]. Various plants and their constituents enhance cognitive function, have a neuroprotective, anti-inflammatory, and antioxidant mechanisms ,along with acetylcholinesterase inhibition, and are known to alleviate other symptoms of AD, including depression, memory loss, and poor cognition [47] [48] . Some of the biologically active ingredients of herbal extracts are tannins, terpenoids, alkaloids and flavonoids. Along with this, the vital focus towards nanotechnology has helped in improving treatments. It was seen that the treatment options for AD are limited mainly due to the inability of the drugs to cross the blood–brain barrier(BBB) [49] [50]. Nanocarriers like synthetic biodegradable polymers are useful to form nano dosage forms which have enhanced solubility and bioavailability, reduced toxicity, and increase the pharmacological activity of the active drug [51]. These nanocarriers may help in increasing the biological activity of the herbal drug and their constituents. Coupled together, they improve solubility, enhance the retention rate of the drug, and with that, the ability to permeate through the blood brain barrier [52].

Curcumin encapsulated PLGA nanoparticles(NPs) were prepared by emulsion solvent evaporation method in a study [53]. The NPs potentially induced neuronal stem cell (NSC) proliferation and neuronal differentiation in vitro and in the hippocampus and subventricular zone of adult rats, in comparison with uncoated bulk curcumin. These nanoparticles were seen to reverse learning and memory impairments in an amyloid beta-induced rat model of AD-like phenotypes, by inducing neurogenesis through activation of the canonical Wnt/β-catenin pathway. Hence, it may offer a therapeutic approach for the treatment of Alzheimer's disease.

In another study, a quercetin (Qu) modified polysorbate 80 (P-80)-coated gold palladium (AuPd) core-shell structure was synthesized. The study conducted was to check the the activation of autophagy which eliminates the intracellular amyloid-β (Aβ) and slows down the neurotoxicity induced by Aβ [54]. The results of the study indicated that concave cubic Qu-P-80-AuPd activated the autophagy of SH-SY5Y cells, accelerated the clearance of Aβ, and protected SH-SY5Y cells from Aβ-induced cytotoxicity damage. Piperine (PIP) is a natural alkaloid with memory enhancement abilities. In a study [55], Tween-modified monoolein cubosomes (T-cubs) were used as nanocarriers for PIP. The results revealed T-cubs had the potential to significantly enhance PIP cognitive effects and even restore cognitive function to normal levels. T-cubs showed potential anti-inflammatory and anti-apoptotic activity of loaded PIP, indicating the potential to stop the progression of AD. Hear in Table 1 we listed 50 phytoconstituents with their biological sources along with the nano herbal formulation.

CONCLUSION

Alzheimer's is the 3rd leading cause of death, whereas treatment of AD is a major challenge due to the presence of BBB. Cholinesterase inhibitors are used for the treatment of AD, which cannot completely cure the disease. Numerous evidence suggests that phytoconstituents show neuroprotective effects for the treatment of AD. However, poor permeability and low bioavailability minimise their potential. To overcome these limitations, researchers worked with nanotechnology, and research suggested that nanoparticles improved drug permeability and bioavailability. Currently, researchers are showing more interest in phytoconstituents and their nano-herbal formulations for the effective treatment of AD. Nanoparticles have proven their potency. However, further study is required to make them more essential. Additionally, the clinical efficacy

of nanoparticles for AD needs long-term assessments for the design of nano formulations with more specificity.

CONSENT FOR PUBLICATION
Not applicable.

FUNDING
None

CONFLICT OF INTEREST
The author declares no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS
Declared none

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