REVIEW ARTICLE

Herbal Extract Nano-formulation for Huntington's disease Treatment

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Abstract

The hallmark of Huntington's disease (HD), an autosomal dominant genetic disorder, is degeneration of neurons of central nervous system (CNS). Tranquilizers, antipsychotics, antidepressants, and monoamine depletors are among the often utilized in treatments. These medications, however, are unable to stop the behavioral, cognitive, and psychotic disorders linked to HD. Moreover, their long-term negative effects restrict their continuous use. Still, due to their limited drug solubility and penetration to the target site, herbal medicines are unable to advance the phase of clinical investigation. Herbal formulation and extracts that show potential in neurotoxic HD models must have their active ingredients and underlying mechanisms of action thoroughly investigated. Several plants that are known to be CNS-active medications, such as *Bacopa monnieri*, *Ginkgo biloba*, *Panax ginseng*, *Cannabis sativa,* and *Curcuma longa L.* were listed as the most promising anti-HD options. In the past few decades, it has been a paradigm shift in research toward the creation of nanoformulations based on herbal medications that can improve their permeability through blood-brain barrier and bioavailability. This review addresses the phytomedicines investigated against HD, current clinical studies on herbal medications used only for HD treatment, and the possible neuroprotective effects of these drug's nanocarriers.

Key words: Huntington's disease, nanoformulations, herbal extracts, neurodegenerative disorder, nano-phytomedicines

INTRODUCTION

Every year, neurodegenerative disorders afflict millions of people globally. The progressive degeneration and malfunction of neurosis are characteristic of neurodegenerative illnesses. Protein degradation,[1,2] different environmental variables,[3] mitochondrial problems,[4] genetic background,[5,6] odd protein accumulation in neurons,[5] etc. are some of the causes of neurodegenerative disorders.[6] However, one of the main issues with neurodegenerative diseases is aging.[7]

Huntington's disease (HD) is autosomal-dominant neurodegenerative disorder that is inherited genetically and affects muscle coordination. It results in a progressive degeneration of neurons, chorea, cognitive impairment, motor ataxia, dystonia, and psychological problems.[8] The majority of affected individuals have symptoms between the ages of 35 and 45 in their mid-adult years,[9] while the condition may start earlier in life. The illness's unusual jerky, uncontrollable writhing motions are known as Chorea.[10] The first exon of the disease, the IT15(Htt) gene, which codes for the protein huntingtin (Htt), contains an autosomal dominant mutation known as the unstable expanded cytosine-adenine-guanine triplet repeat.[11] This mutation causes HD and results in a mutant polyglutamine (polyQ) strand of variable length at the N-terminus of the mutant huntingtin (mHtt).[9,10] This malfunction has a role in how HD's clinical symptoms manifest. Behavioral and mental health problems are treated with a traditional therapy approach since there is no treatment to case off the progression of neuronal damage.[9,12] In the central nervous system (CNS), this may result in the loss of neurons and the degradation of neurotransmitters.[13] Affected individuals typically pass away 15–20 years after experiencing their initial symptoms.[14] Patients with HD have a variety of biochemical changes, including downregulation of γ-aminobutyric acid (GABA) and acetylcholine (ACh), also a decrease in the enzymes that produce substances,

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namely, glutamate decarboxylase and choline-acetyl transferase, respectively.[13,15,16] According to studies, among the non-pharmacological treatments for HD which are most effective are therapy, genetic counseling, and palliative care.[8] It has also been noted that the suicide rate among HD patients and those who care for them is higher than that of the general community. This disparity was attributed to suicide that was reasonable and unrelated to mental illness.[17] Only 3–7 people/100,000 are affected by HD globally, and 20 out of every 100,000 are carriers.[10]

Even after HD's genetics were identified 20 years ago, the pathophysiology remains poorly understood, and no effective treatment has yet to be found. According to studies, there are not many therapy options available to address HD's cognitive, psychological, and motor symptoms.[18] Tetrabenazine, the sole medication for chorea, is recognized for its drawbacks, including adverse effects and drug interactions.[19] Efficacious treatment for early HD symptoms has been described for mood stabilizers and selective serotonin reuptake inhibitors.[18,20,21]

NATURAL NEUROPROTECTIVE DRUG

Complex mixes of organic compounds and phytoconstituents, such as alkaloids, flavonoids, glycosides, saponins, fatty acids, sterols, and terpenes, are found in herbal medicines. Certain herbal medications contain phytoconstituents that have demonstrated pharmacological efficacy in mitigating HD symptoms. Traditional Indian herbal medicines have been utilized to treat a variety of nervous system disorders. The Sanskrit word *vatavyadh* (neuropathic illness) describes this condition. Vata is the energy that surrounds the body; any disruption to this flow is referred to as *VataVyadh.* At the end, it causes chorea, weakness, hypersensitivity, and dementia.[22]

Several innovative technologies have been developed in the last few decades with the specific goal of delivering a vast array of different chemicals and bioactive molecules to mitochondria. The advancement of intracellular penetration, pharmacological effects distribution at the target location, and drug pharmacokinetic profile, have been made possible by these nanotechnology.[23] A lot of focus has been placed on creating effective drug delivery systems using materials that are nanoscale (sizes ranging from 1 to 100 nm), which can pass through various biological barriers, prevent drugs from deactivating too soon, which enhances their pharmacokinetic profile, and promote the distribution of the target molecules at the target site and internalization.[24] Numerous investigations are conducted to create nanoformulations of natural chemicals, however, it is still unclear if the activity of the nano-encapsulated substance is similar to that of the raw material. Numerous studies have addressed this.

The herbal medicines and natural compound nanoformulations are compiled in Table 1.

Rauwolfia alkaloid reserpine[37-39] and the belladonna root and its alkaloids[40,41] and the have been shown to be beneficial in the treatment of HD in some early literature. The use of botanic and products containing from herbs has garnered more attention recently in regards to both the avoidance and mitigation of HD.

The rhizome of *Curcuma longa L*. (*Zingiberaceae*) is the source of curcumin, a dietary polyphenol having an good safety profile that has significant value as an antioxidant, anti-inflammatory, and anti-cancer agent.[42,43] According to Sandhir *et al*., *in vivo* HD model, curcumin-encapsulated solid lipid nanoparticles (C-SLNs) reduced mitochondrial dysfunction and improved neuromotor coordination.[33] In the treatment of spinal cord injury,[44] traumatic brain injury,[45] bipolar disorder,[46] Parkinson's disease (PD)[47] etc., curcumin's neuroprotective impact has also been shown. Curcumin had inadequate pharmacokinetics, with limited absorption, minimal bioavailability, and rapid bodily disposal, despite its remarkable therapeutic capabilities. Different NPs, nanomicelles, nanocapsules, and nanoliposomes were created to increase Curcumin's pharmacokinetics and bioavailability to address these flaws.[48] Chronic treatment of curcumin has been reported in one study to continually raise body weight and increase succinate dehydrogenase cell enzyme activity in rats given with 3-nitropropionic acid (3-NP).[49] Furthermore to its potent antioxidant properties, curcumin's reversed 3-NP-induced cognitive and motor deficits suggest that it might be useful in treating HD.[49]

Bacopa monnieri (BM), also known as *Herpestis monniera* or Brahmi, is a member of the *Scrophulariaceae* family. It is known as *Medhya rasayana* in Ayurveda and is found all over the Indian subcontinent.[50-52] It improves memory and is used to treat anxiety, insomnia, and epilepsy.[53,54] Tri-terpenoid saponins, such as dammarane and bacosides A and B, are the plant's important chemical constituents.[55,56] Apart from these important constituents, it also contains additional saponins, such as N1 and N2,jujubogenin, pseudojujubogenin,[57] bacopaside I-V, X, and bacopa saponin A-G.[58] The herb also contains monnieri, herpestine, and brahmine.[59,60] In addition, it lowers levels of free fatty acids, malondialdehyde, and reactive oxygen species (ROS).[61] By improving thiol-related antioxidant compounds and antioxidant enzyme activity, oral ingestion of BM's leaves powder has been shown to lower basal concentrations of various oxidative indicators and indicate a considerable antioxidant capacity. Dietary supplements containing BM have been proven to offer significant protection against the oxidative harm that neurotoxins in the brain can produce.[53] Due to its above protective impact against neural dysfunctions caused by stress, BM has also been demonstrated to be beneficial in the treatment of HD.[62] In rats, 3-NP-induced HD was reduced by CSLNs. Antioxidant enzyme activities (such as SOD and glutathione) were significantly increased in rats treated with CSLNs, whereas lipid peroxidation, protein carbonyls, ROS, and mitochondrial swelling were significantly reduced.[35]

Table 1: Nanoformulations of herbal compounds

Nanoformulations	Herbal compound	Method	Activity	Reference
Nanoparticles	Curcumin	PLGA particles loaded with curcumin using the emulsion-diffusion-evaporation method	Pro-inflammatory activity	[25-30]
		NPs encapsulated with curcumin by nanoprecipitation		
		Polycationic cross-linking through emulsion polymerization and ionotropic pre-gelation encapsulated curcumin using alginate, chitosan, and Pluronic polymers		
Nanoparticles	*Panax ginseng*	Silver and Gold nanoparticles produced by green synthesis using extract of Ginseng root prepared by high-energy ball milling	Scavenge free radicals and Boost immunity, energy, vitality	[31,32]
Polymeric Nanomicelles	Curcumin	Solid dispersion method	Improve Bioavailability	[33]
Nanofiber	Curcumin	Curcumin-loaded cellulose acetate fibers synthesized through electrospinning	Pro-inflammatory activity	[34]
Solid lipid NP	Curcumin	curcumin-encapsulated SLN	Reduced mitochondrial dysfunction and improve neuromotor coordination	[35]
Nanoparticles	cannabidiol	Cannabidiol Coated by Nano-Chitosan	learning, memory and reduces Aβ plaque formation	[36]

The genus cannabis comprises flowering plants such as *Cannabis sativa* (often known as hemp or ganja) and allied species that are indigenous to South and Central Asia. Within the CNS, the cannabinoid (CB) system is widely distributed and regulates a different kind of neurophysiological functions, including pain, hunger, and cognition. Isolated from cannabis, phytocannabinoids target endogenous CB molecules as well as the G-protein coupled CB receptors CB(1) and CB(2).[63] The two primary constituents of *C. sativa* are Δ(9)-Tetrahydrocannabinol (Δ-9-THC) and cannabidiol (CBD).[64] In 3-NP-intoxicated rat models of HD, botanical extracts rich in Δ(9)-THC and/or CBD (1:1) inhibited GABA deficit and altered the expression of neural and biochemical markers.[65] In various preclinical HD models, CBs functioned as disease-modifying drugs and reduced hyperkinetic symptoms due to their, neuroprotective, anti-inflammatory, and neuroregenerative qualities. A clinical trial for Sativex®, a mixture of CBD and/or Δ(9)-THC, is almost ready to begin against HD.[66] CBD and/orΔ(9)-THC have shown opposing effects on psychopathology and human neuronal function in one study.[64] CBD was discovered to stimulate the paralimbic and limbic regions of the brain, but Δ(9)-THC seemed to have potential effects on other parts of brain.[67]

For over 2,000 years, *Panax ginseng* (PG) root, a herb that has been utilized as a tonic in Japan, China, and Korea to revive and replenish an appropriate body metabolism.[68] Asian and American ginseng (*Panax1 quinquefolium* L.) belong to the *Araliaceae* family and are the very common species of PG. Due to its neuroprotective properties, PG is used to treat and prevent neurodegenerative illnesses such PD, AD, HD, strokes, and signs of depression.[69] The active ingredients in PG are ginsenosides, saponin glycosides, triterpenoids, and tetracyclic dammarane.[70,71] The effect of ginsenosides in preventing NDs like HD, PD, and AD has been the subject of several studies published in recent years. In addition, several of the clinical trials on PG and its components, gintonin, and ginsenosides showed positive findings, indicating its safety.[72] Through the inhibition of excitotoxicity and excessive Ca2+ influx into neurons, it aids in the reduction of lipid peroxidation. It helps to improve cognitive function by maintaining neuronal structural integrity and cellular ATP concentrations hence it may effectively help in HD.[73] It has been observed that ginsenosides Rb3 and Rg1 protect cortical neurons from glutamate-induced cell death by blocking Ca2+ influx through glutamate receptors.[74] Saponins, which are N-methyl-D-aspartate (NMDA) glutamate antagonists, are found in ginseng. They lessen the amount of intracellular Ca2+ influx in the hippocampal region, which inhibits glutamate-type NMDA receptors and lessens HD symptoms.[74] Ginsenosides Rb3, Rb1, and Rd demonstrated

Table 2: Formulation of phytoconstituents and duration of study

Phytoconstituents	Formulation and composition	Animal Model, No. of Animal, Dose (mg/kg)	Duration	Results and applications	Reference
Curcumin	SLNs formulated with lecithin taurocholate, Steric acid, Curcumin	20 female Wistar Rat, 40 mg/kg p.o.	7 days	Oral bioavailability of curcumin was enhanced by SLNs and evaluated its neuroprotective effectiveness against HD caused by 3-NP	[35]
poly (trehalose)	Polymeric nanoparticle formulated	Transgenic mice for HD 0.4 mg/mL corresponding to 50 μM Trehalose, i.p.	56 days and 84 days	Polymeric nanoparticles increased the trehalose BBB permeability for Neuroprotective effects	[82]
Thymoquinone	SLN formulated with lecithin taurocholate, Thymoquinone, Steric acid	48 Albino male rats, with doseTQ-SLNs (40,80 mg/kg) p.o., TQ-SLNs (10, 20 mg/kg),	15 days	Thymoquinone's bioavailability, absorption and solubility were all enhanced by SLNs. In addition, it improved drug payload and prolonged drug release abilities. Thymoquinone in SLNs thus functions as an inhibitor for 3-NP-induced degeneration and inflammation.	[83]

a neuroprotective effect on 3-NP-induced striatal neuronal damage.[75]

NEED OF NOVEL DRUG DELIVERY OF NATURAL NEUROPROTECTIVE DRUGS

Although there is no doubt that herbal drugs have excellent neuroprotective properties, they are limited by factors like low bioavailability, poor aqueous solubility, and absence of permeability across the blood-brain barrier (BBB). However, it had been demonstrated that modern drug delivery methods enhance therapeutic stability, effectiveness, bioavailability, and brain permeability (BBB)[76,77] The herbal drugs while also minimizing their adverse effects feat that are difficult to accomplish with traditional drug delivery systems.[77,78] Due to their smallest particle size (below 200 nm), which allows them to pass BBB endothelial cells by transcytosis, herbal constituents derived nanoparticles have been found to minimize first-pass metabolism and improve their bioavailability. Receptor-mediated transcytosis can be improved by lactoferrin receptors, transferrin receptor ligands, albumin transporters, or glucose transporter 1 (GLUT1).[79,80] Numerous research have demonstrated that plant extracts or their active ingredients improve pharmacokinetic characteristics like Cmax and AUC, which increases the oral bioavailability of the product. As a result, they are now capable of treating several kinds of NDs, such as PD, HD, and AD. It is significant to highlight that the information that is currently available about the formulation of nanoparticles for the treatment of HD is restricted to pre-clinical research. However, given that NDDS has been successful in treating neurodegenerative disorders other than HD, it is expected that they will also be successful in treating HD. To treat HD, it is imperative to investigate delivery systems that have been filled with the aforementioned phytoconstituents and/or extracts. However, certain studies that had proven to treat HD are covered in following section of this review.

POLYMERIC NANOPARTICLES

Polymeric nanoparticles have a particle size that is about between 10 and 1000 nm. Both nanospheres and nanocapsules can be created from them. A matrix system makes up nanospheres. The medicine is inserted into the polymeric membrane-filled cavity of a nanocapsule.[81] According to Debnath *et al*., trehalose was successfully delivered by increasing the BBB permeability using poly(trehalose) nanoparticles. It has been found that poly(trehalose) nanoparticles exhibit greater potency in comparison to trehalose molecules. In an *in vitro* investigation, they were discovered to prevent polyQ aggregation in HD150Q cells. Poly(trehalose) nanoparticles repressed mHTT genes and decreased polyQ levels and amyloid aggregation, as shown by immunoblot and Dot blot analyses.[82]

Formulation of phytoconstituents and duration of study with results and application is given in Table 2.

SLNS

SLNs are composed of a solid lipid matrix stabilized by physiological lipids and emulsifier molecules. The process of homogenization, which reduces size of drug particles by applying high pressure and temperature due to mechanical and thermodynamic stress, is used to prepare SLNs.[84,85] SLNs are very biocompatible and work well as nanocarriers to increase the bioavailability of medications. High pressure homogenization allows for the creation of SLNs with sizes ranging from 0 to 1000 nm. By endocytosis, those between the sizes of 120 and 200 nm can readily pass through the BBB's endothelial cells.[86] When SLNs bind to a ligand (such as apolipoprotein E), their brain permeability can be increased.[87] The low entrapment efficiency and low drug loading capacity of SLNs are its limitations. Sandhir *et al*. showed that C-SLNs demonstrated efficaciousness against 3-NP-induced HD rats in one of their investigations. In this trial, a medication at doses of 20 mg and 40 mg/kg was taken orally for 7 days. The homogenization process was used to prepare C-SLNs. Curcumin, lecithin taurocholate, and steric acid were employed in this formulation. The formulation demonstrated neuroprotective effects against neurotoxic (3-NP) that were considerably dose-dependent. In addition, it significantly increased the striatum's levels of mitochondrial cytochrome and spontaneous locomotor activity in total photobeam counts of 3-NP-induced HD animals.[35]

The pharmacological activity of thymoquinone (TQ) has been mentioned by the authors in another investigation. In addition to being a potent antioxidant, it prevents neuroinflammation. The drug has low solubility, which results in decreased drug absorption and bioavailability prohibited it from showing its desired effect in the *in vivo* trial. As a result, the drug cannot concentrate in the targeted area (the brain) to the necessary level.[88] TQ-SLNs were obtained by Ramachandran *et al*. to increase the drug's brain permeability and bioavailability.[4,83] The homogenization process was used to prepare TQ-SLNs. Polymerase chain reaction was used to test the inflammatory response, and TQ-SLNs demonstrated anti-inflammatory properties. It was discovered that Interleukin-1 beta, tumor necrosis factor alpha, IL-6, COX2, and iNOS are among the inflammatory mediators that TQ suspension and TQ-SLNs had suppressed.

NANOLIPOSOMES

Herbal drugs encapsulated in nanoliposomes may be ableavoid a first-pass metabolism, cross the physiological membrane barriers of the body, and increase oral bioavailability due to a submicron dimension of vesicles. Ligand-based nanoliposomes (like GLUT1, lactoferrin, and transferrin) prepared by surface modification methods have proven to distribute multiple proteins, antibodies and peptides.[89] Ligands facilitate the liposomes' transcytosis-induced BBB penetration. Through passive diffusion, nanoliposomes can reach the brain and release medicines that are entrapped there by an energy-dependent process or passive efflux.[89] Liposomes' short half-life is a drawback since it makes it simple for the medication to be metabolized by oxidation and hydrolysis.[90] The impact of curcumin-loaded peptide nanoliposomes produced from apoprotein E (Apo-E) on HD was investigated by Francesca *et al*. The thin film hydration approach has been used to generate the liposomes by loading Apo-E into a dispersion of bovine brain sphingomyelin (Sm), 1,2-stearoyl-sn-glycero-3-phosphoethanolamine-N- [maleimide (poly (ethylene glycol)-2000)] (mal-PEG-PhoEth), and cholesterol (Chol). PDI, zeta potential, and particle size of the produced liposomes were 0.187, −19.41 ± 0.09 mV, and 132 ± 10 nm, respectively. Rat brain endothelial cells were used in the *in vitro* cell line investigation. According to the results of the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay, there was no cytotoxicity shown by the curcumin-nanoliposomes. Confocal laser scanning microscopy was used to detect the cellular uptake of the fluorescently labeled liposomes, which had been labeled with a fluorescent dye. It was discovered that liposomes did not possess cellular intake of fluorescence and membrane accretion in lack of surface functionalization. By interactions with low-density lipoprotein receptors through a unique amino acid sequence in the Apo-E sequence, curcumin-nanoliposomes improved in the treatment of HD. Curcumin was transcytosed across the BBB without being impacted by lysosomal degradation. Thus, the acquired data showed that BBB targeting by ligand-based nanoliposomes succeeded in avoiding drug degradation.[91]

CONCLUSION

Globally, ND prevention is crucial for the elderly population. In this case, phytoconstituents serve as innovative medical treatments. Numerous activities, including anti-proliferative, antioxidant, anti-inflammatory, and anti-apoptotic properties, have been described for herbal medications. It has also been found that several of them lower synaptic AChE levels. As a result, they might provide a useful substitute for the synthetic drugs which are now used for treating HD. The review highlights a number of clinical and preclinical studies that demonstrate significant improvements in the treatment of HD symptoms. Due to their low solubility and pharmacokinetic characteristics, herbal drugs' efficacy has not been well investigated despite having great therapeutic promise. The better bioavailability or direct targeting of natural drugs to particular cells in various nanocarriers, such as polymeric nanoparticles, nanoliposomes, and SLNs, has demonstrated extremely good efficacy in treating HD. This has additionally aided in reducing their dosage and toxicity. Poor drug loading in the formulation, lesser processing stability of herbal pharmaceuticals, and difficulties scaling up the low stability of nanoformulations and process, are the main issues facing the formulation of herbal drug-loaded nanoparticles. Therefore, it is crucial to consider these matters before

initiating pre-clinical research. For their entry into the market, comprehensive clinical research is necessary after obtaining successful pre-clinical reports.

REFERENCES

1. Brown RC, Lockwood AH, Sonawane BR. Neurodegenerative diseases: An overview of environmental risk factors. Environ Health Perspect 2005;113:1250-6.
2. Meek PD, McKeithan K, Schumock GT. Economic considerations in Alzheimer's disease. Pharmacotherapy 1998;18:68-73.
3. Rubinsztein DC. The roles of intracellular protein-degradation pathways in neurodegeneration. Nature 2006;443:780-6.
4. Beal MF. Mitochondria take center stage in aging and neurodegeneration. Ann Neurol 2005;58:495-505.
5. Mosconi L, Brys M, Switalski R, Mistur R, Glodzik L, Pirraglia E, *et al.* Maternal family history of Alzheimer's disease predisposes to reduced brain glucose metabolism. Proc Natl Acad Sci U S A 2007;104:19067-72.
6. Barnham KJ, Masters CL, Bush AI. Neurodegenerative diseases and oxidative stress. Nat Rev Drug Discov 2004;3:205-14.
7. Hung CW, Chen YC, Hsieh WL, Chiou SH, Kao CL. Ageing and neurodegenerative diseases. Ageing Res Rev 2010;9 Suppl 1:S36-46.
8. Phillips W, Shannon KM, Barker RA. The current clinical management of Huntington's disease. Mov Disord 2008;23:1491-504.
9. Walker FO. Huntington's disease. Lancet 2007;369:218-28.
10. Nayak A, Ansar R, Verma SK, Bonifati DM, Kishore U. Huntington's disease: An immune perspective. Neurol Res Int 2011;2011:563784.
11. Bates GP, Dorsey R, Gusella JF, Hayden MR, Kay C, Leavitt BR, *et al.* Huntington disease. Nat Rev Dis Primers 2015;1:15005.
12. Ross CA, Aylward EH, Wild EJ, Langbehn DR, Long JD, Warner JH, *et al.* Huntington disease: Natural history, biomarkers and prospects for therapeutics. Nat Rev Neurol 2014;10:204-16.
13. Li X, Valencia A, Sapp E, Masso N, Alexander J, Reeves P, *et al.* Aberrant Rab11-dependent trafficking of the neuronal glutamate transporter EAAC1 causes oxidative stress and cell death in Huntington's disease. J Neurosci 2010;30:4552-61.
14. Choudhary S, Kumar P, Malik J. Plants and phytochemicals for Huntington's disease. Pharmacogn Rev 2013;7:81-91.
15. Dey A, Nandy S, Mukherjee A, Pandey DK. Plant Natural Products as Neuroprotective Nutraceuticals: Preclinical and Clinical Studies and Future Implications. Vol. 90. In: Proceedings of the National Academy of Sciences, India Section B: Biological Sciences; 2020. p. 929-43.
16. Pareek H, Thakur P, Ray DJ. Modeling and docking studies of 4-aminobutyrate aminotransferase for Huntington's disease. Int J Pharma Bio Sci 2011;2:539-49.
17. Halpin M. Accounts of suicidality in the Huntington disease community. Omega (Westport) 2012;65:317-34.
18. Killoran A, Biglan KM. Current therapeutic options for Huntington's disease: Good clinical practice versus evidence-based approaches? Mov Disord 2014;29:1404-13.
19. Setter SM, Neumiller JJ, Dobbins EK, Wood L, Clark J, DuVall CA, *et al.* Treatment of chorea associated with Huntington's disease: Focus on tetrabenazine. Consult Pharm 2009;24:524-37.
20. Frank S, Jankovic J. Advances in the pharmacological management of Huntington's disease. Drugs 2010;70:561-71.
21. Mestre TA, Ferreira JJ. An evidence-based approach in the treatment of Huntington's disease. Parkinsonism Relat Disord 2012;18:316-20.
22. Rao RV, Descamps O, John V, Bredesen DE. Ayurvedic medicinal plants for Alzheimer's disease: A review. Alzheimers Res Ther 2012;4:22.
23. Couvreur P, Vauthier C. Nanotechnology: Intelligent design to treat complex disease. Pharm Res 2006;23:1417-50.
24. Gruber J, Fong S, Chen CB, Yoong S, Pastorin G, Schaffer S, *et al.* Mitochondria-targeted antioxidants and metabolic modulators as pharmacological interventions to slow ageing. Biotechnol Adv 2013;31:563-92.
25. Anand P, Nair HB, Sung B, Kunnumakkara AB, Yadav VR, Tekmal RR, *et al.* RETRACTED: Design of Curcumin-Loaded PLGA Nanoparticles Formulation with Enhanced Cellular Uptake, and Increased Bioactivity *in Vitro* and Superior Bioavailability *in Vivo*. Netherlands: Elsevier; 2010.
26. Das RK, Kasoju N, Bora U. Encapsulation of curcumin in alginate-chitosan-pluronic composite nanoparticles for delivery to cancer cells. Nanomedicine 2010;6:153-60.
27. Duan J, Zhang Y, Han S, Chen Y, Li B, Liao M, *et al.* Synthesis and *in vitro/in vivo* anti-cancer evaluation of curcumin-loaded chitosan/poly(butyl cyanoacrylate) nanoparticles. Int J Pharm 2010;400:211-20.
28. Shaikh J, Ankola DD, Beniwal V, Singh D, Kumar MN. Nanoparticle encapsulation improves oral bioavailability of curcumin by at least 9-fold when compared to curcumin administered with piperine as absorption enhancer. Eur J Pharm Sci 2009;37:223-30.
29. Suwantong O, Opanasopit P, Ruktanonchai U, Supaphol PJ. Electrospun cellulose acetate fiber mats containing curcumin and release characteristic of the herbal substance. Polymer 2007;48:7546-57.
30. Yallapu MM, Gupta BK, Jaggi M, Chauhan SC. Fabrication of curcumin encapsulated PLGA nanoparticles for improved therapeutic effects in metastatic cancer cells. J Colloid Interface Sci 2010;351:19-29.
31. Lee SB, Yoo S, Ganesan P, Kwak HS. Physicochemical and antioxidative properties of Korean nanopowdered

white ginseng. Food Sci Technol 2013;48:2159-65.
32. Wen HW, Li WC, Chung RJ, Yin SY, Chou TH, Hsieh PC, *et al.* Evaluation of nanofabricated ginseng extract powders. J Nanosci Nanotechnol 2009;9:4108-15.
33. Song L, Shen Y, Hou J, Lei L, Guo S, Qian CJ, *et al.* Polymeric micelles for parenteral delivery of curcumin: Preparation, characterization and *in vitro* evaluation. Colloids Surf A Physicochem Eng Aspects 2011;390:25-32.
34. Brahatheeswaran D, Mathew A, Aswathy RG, Nagaoka Y, Venugopal K, Yoshida Y, *et al.* Hybrid fluorescent curcumin loaded zein electrospun nanofibrous scaffold for biomedical applications. Biomed Mater 2012;7:045001.
35. Sandhir R, Yadav A, Mehrotra A, Sunkaria A, Singh A, Sharma S. Curcumin nanoparticles attenuate neurochemical and neurobehavioral deficits in experimental model of Huntington's disease. Neuromolecular Med 2014;16:106-18.
36. Amini M, Abdolmaleki Z. 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 2022;81:171-83.
37. Vorisek V. Reserpine treatment of Huntington's chorea & other extrapyramidal syndromes. Cesk Neurol 1958;21:99-105.
38. Chhuttani PN, Singh S. Reserpine in Huntington's chorea. J Indian Med Assoc 1959;32:402-3.
39. Zmorski TJ. Reserpine (serpasin) in therapy of Huntington's chorea. Psychiatr Neurol (Basel) 1959;137:40-8.
40. Tomlinson PJ. The treatment of Huntington's chorea with belladonna alkaloids. Psychiatr Q 1947;21:447-52.
41. Lazar MJ. The use of Bulgarian Belladonna root in the treatment of Huntington's chorea. Curr Pharm Des 1948;22:136-40.
42. Basnet P, Skalko-Basnet NJ. Curcumin: An anti-inflammatory molecule from a curry spice on the path to cancer treatment. Molecules 2011;16:4567-98.
43. Noorafshan A, Ashkani-Esfahani SJ. A review of therapeutic effects of curcumin. Curr Pharm Des 2013;19:2032-46.
44. Kim KT, Kim MJ, Cho DC, Park SH, Hwang JH, Sung JK, *et al.* The neuroprotective effect of treatment with curcumin in acute spinal cord injury: Laboratory investigation. Neurol Med Chir (Tokyo) 2014;54:387-94.
45. Samini F, Samarghandian S, Borji A, Mohammadi GJ, Bakaian M. Curcumin pretreatment attenuates brain lesion size and improves neurological function following traumatic brain injury in the rat. Pharmacol Biochem Behav 2013;110:238-44.
46. Gazal M, Valente MR, Acosta BA, Kaufmann FN, Braganhol E, Lencina CL, *et al.* Neuroprotective and antioxidant effects of curcumin in a ketamine-induced model of mania in rats. Eur J Pharmacol 2014;724:132-9.
47. Qualls Z, Brown D, Ramlochansingh C, Hurley LL, Tizabi YJ. Protective effects of curcumin against rotenone and salsolinol-induced toxicity: Implications for Parkinson's disease. Neurotox Res 2014;25:81-9.
48. Bollimpelli VS, Kumar P, Kumari S, Kondapi AK. Neuroprotective effect of curcumin-loaded lactoferrin nano particles against rotenone induced neurotoxicity. Neurochem Int 2016;95:37-45.
49. Frautschy SA, Hu W, Kim P, Miller SA, Chu T, Harris-White ME, *et al.* Phenolic anti-inflammatory antioxidant reversal of Abeta-induced cognitive deficits and neuropathology. Neurobiol Aging 2001;22:993-1005.
50. Gohil KJ, Patel JA. A review on *Bacopa monniera*: Current research and future prospects. Int J Green Pharm 2010;4(1).
51. Dey A, Hazra A, Nongdam P, Nandy S, Tikendra L, Mukherjee A, *et al.* Enhanced bacoside content in polyamine treated *in-vitro* raised *Bacopa monnieri* (L.) Wettst. S Afr J Bot 2019;123:259-69.
52. Nandy S, Mukherjee A, Pandey DK, Dey AJ. *Bacopa monnieri*: The Neuroprotective Elixir from the East-Phytochemistry, Pharmacology, and Biotechnological Improvement. Berlin: Springer; 2020. p. 97-126.
53. Shinomol GK, Muralidhara. *Bacopa monnieri* modulates endogenous cytoplasmic and mitochondrial oxidative markers in prepubertal mice brain. Phytomedicine 2011;18:317-26.
54. Calabrese C, Gregory WL, Leo M, Kraemer D, Bone K, Oken B. Effects of a standardized *Bacopa monnieri* extract on cognitive performance, anxiety, and depression in the elderly: A randomized, double-blind, placebo-controlled trial. J Altern Complement Med 2008;14:707-13.
55. Russo A, Borrelli F. *Bacopa monniera*, a reputed nootropic plant: An overview. Phytomedicine 2005;12:305-17.
56. Bammidi SR, Volluri SS, Chippada SC, Avanigadda S, Vangalapati MJ. A review on pharmacological studies of *Bacopa monniera.* J Chem Bio Phy Sci 2011;1:250-9.
57. Hou CC, Lin SJ, Cheng JT, Hsu FL. Bacopaside III, bacopasaponin G, and bacopasides A, B, and C from *Bacopa monniera*. J Nat Prod 2002;65:1759-63.
58. Garai S, Mahato SB, Ohtani K, Yamasaki K. Dammarane-type triterpenoid saponins from *Bacopa monniera*. Phytochemistry 1996;42:815-20.
59. Kawai KI, Shibata SJ. Pseudojujubogenin, a new sapogenin from *Bacopa monniera.* Phytochemistry 1978;17:287-9.
60. Chakravarty AK, Garai S, Masuda K, Nakane T, Kawahara N. Bacopasides III-V: Three new triterpenoid glycosides from *Bacopa monniera*. Chem Pharm Bull (Tokyo) 2003;51:215-7.
61. Kim GW, Copin JC, Kawase M, Chen SF, Sato S, Gobbel GT, *et al.* Excitotoxicity is required for induction of oxidative stress and apoptosis in mouse striatum by the mitochondrial toxin, 3-nitropropionic acid. J Cereb Blood Flow Metab 2000;20:119-29.
62. Bhattacharya SK, Bhattacharya A, Kumar A, Ghosal SJ. Antioxidant activity of *Bacopa monniera* in rat frontal

cortex, striatum and hippocampus. Phytother Res 2000;14:174-9.
63. Gowran A, Noonan J, Campbell VA. The multiplicity of action of cannabinoids: Implications for treating neurodegeneration. CNS Neurosci Ther 2011;17:637-44.
64. Bhattacharyya S, Morrison PD, Fusar-Poli P, Martin-Santos R, Borgwardt S, Winton-Brown T, *et al.* Opposite effects of Δ-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. Neuropsychopharmacology 2010;35:764-74.
65. Sagredo O, Pazos MR, Satta V, Ramos JA, Pertwee RG, Fernández-Ruiz J. Neuroprotective effects of phytocannabinoid-based medicines in experimental models of Huntington's disease. J Neurosci Res 2011;89:1509-18.
66. Sagredo O, Pazos MR, Valdeolivas S, Fernandez-Ruiz J. Cannabinoids: Novel medicines for the treatment of Huntington's disease. Recent Pat CNS Drug Discov 2012;7:41-8.
67. Fusar-Poli P, Crippa JA, Bhattacharyya S, Borgwardt SJ, Allen P, Martin-Santos R, *et al.* Distinct effects of Δ9-tetrahydrocannabinol and cannabidiol on neural activation during emotional processing. Arch Gen Psychiatry 2009;66:95-105.
68. Nah SY, Kim DH, Rhim H. Ginsenosides: Are any of them candidates for drugs acting on the central nervous system? CNS Drug Rev 2007;13:381-404.
69. Flanagan E, Lamport D, Brennan L, Burnet P, Calabrese V, Cunnane SC, *et al.* Nutrition and the ageing brain: Moving towards clinical applications. Ageing Res Rev 2020;62:101079.
70. Liu CX, Xiao PG. Recent advances on ginseng research in China. J Ethnopharmacol 1992;36:27-38.
71. Rausch WD, Liu S, Gille G, Radad K. Neuroprotective effects of ginsenosides. Acta Neurobiol Exp (Wars) 2006;66:369-75.
72. Rajabian A, Rameshrad M, Hosseinzadeh H. Therapeutic potential of *Panax ginseng* and its constituents, ginsenosides and gintonin, in neurological and neurodegenerative disorders: A patent review. Expert Opin Ther Pat 2019;29:55-72.
73. Radad K, Gille G, Liu L, Rausch WD. Use of ginseng in medicine with emphasis on neurodegenerative disorders. J Pharmacol Sci 2006;100:175-86.
74. Kim YC, Kim SR, Markelonis GJ, Oh TH. Ginsenosides Rb1 and Rg3 protect cultured rat cortical cells from glutamate-induced neurodegeneration. J Neurosci Res 1998;53:426-32.
75. Lian XY, Zhang Z, Stringer JL. Protective effects of ginseng components in a rodent model of neurodegeneration. Ann Neurol 2005;57:642-8.
76. Lockman PR, Mumper RJ, Khan MA, Allen DD. Nanoparticle technology for drug delivery across the blood-brain barrier. Drug Dev Ind Pharm 2002;28:1-13.
77. Garbayo E, Ansorena E, Blanco-Prieto MJ. Brain drug delivery systems for neurodegenerative disorders. Curr Pharm Biotechnol 2012;13:2388-402.
78. Wang S, Su R, Nie S, Sun M, Zhang J, Wu D, *et al.* Application of nanotechnology in improving bioavailability and bioactivity of diet-derived phytochemicals. J Nutr Biochem 2014;25:363-76.
79. Betzer O, Shilo M, Opochinsky R, Barnoy E, Motiei M, Okun E, *et al.* The effect of nanoparticle size on the ability to cross the blood-brain barrier: An *in vivo* study. Nanomedicine (Lond) 2017;12:1533-46.
80. Wiley DT, Webster P, Gale A, Davis ME. Transcytosis and brain uptake of transferrin-containing nanoparticles by tuning avidity to transferrin receptor. Proc Natl Acad Sci U S A 2013;110:8662-7.
81. Jawahar N, Meyyanathan SJ. Polymeric nanoparticles for drug delivery and targeting: A comprehensive review. Int J Health Allied Sci 2012;1:217.
82. Debnath K, Pradhan N, Singh BK, Jana NR, Jana NR. Poly(trehalose) Nanoparticles prevent amyloid aggregation and suppress polyglutamine aggregation in a Huntington's disease model mouse. ACS Appl Mater Interfaces 2017;9:24126-39.
83. Ramachandran S, Thangarajan S. Thymoquinone loaded solid lipid nanoparticles counteracts 3-Nitropropionic acid induced motor impairments and neuroinflammation in rat model of Huntington's disease. Metab Brain Dis 2018;33:1459-70.
84. Battaglia L, Gallarate M. Lipid nanoparticles: State of the art, new preparation methods and challenges in drug delivery. Expert Opin Drug Deliv 2012;9:497-508.
85. Mishra V, Bansal KK, Verma A, Yadav N, Thakur S, Sudhakar K, *et al.* Solid lipid nanoparticles: Emerging colloidal nano drug delivery systems. Pharmaceutics 2018;10:191.
86. Gastaldi L, Battaglia L, Peira E, Chirio D, Muntoni E, Solazzi I, *et al.* Solid lipid nanoparticles as vehicles of drugs to the brain: Current state of the art. Eur J Pharm Biopharm 2014;87:433-44.
87. Michaelis K, Hoffmann MM, Dreis S, Herbert E, Alyautdin RN, Michaelis M, *et al.* Covalent linkage of apolipoprotein e to albumin nanoparticles strongly enhances drug transport into the brain. J Pharmacol Exp Ther 2006;317:1246-53.
88. Odeh F, Ismail SI, Abu-Dahab R, Mahmoud IS, Al Bawab A. Thymoquinone in liposomes: A study of loading efficiency and biological activity towards breast cancer. Drug Deliv 2012;19:371-7.
89. Noble GT, Stefanick JF, Ashley JD, Kiziltepe T, Bilgicer B. Ligand-targeted liposome design: Challenges and fundamental considerations. Trends Biotechnol 2014;32:32-45.
90. Himanshu A, Sitasharan P, Singhai AJ. Liposomes as drug carriers. Int J Pharm Life Sci 2011;2:945-51.
91. Re F, Cambianica I, Zona C, Sesana S, Gregori M, Rigolio R, *et al.* Functionalization of liposomes with ApoE-derived peptides at different density affects cellular uptake and drug transport across a blood-brain barrier model. Nanomedicine 2011;7:551-9.

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