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Recent updates on novel drug delivery systems for herbal drugs against neurodegenerative disease

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Abstract
Many neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis and psychiatric disorders, occur as a result of progressive degeneration or death of neuron cells. There are many herbal drugs having efficacy in neurodegenerative diseases. Modern phytopharmaceutical research can facilitate brain targeting of herbal medicines in the form of Novel Drug delivery System (NDDS) like nanoparticles, microemulsions, matrix systems, solid dispersions, liposomes, phytosomes, transdermal drug delivery systems, and ethosomes. NDDS may play a vital role to cross the blood-brain barrier in neurodegenerative disorders. Nowadays the number of NDDS has been developed to achieve controlled and targeted drug delivery in the bloodstream. NDDS also opens a new door for delivery of herbal drugs at accurate concentration, a study of the mechanism of action and provide a scientific way for standardization of herbal drugs. The present review highlights the existing status of the development of novel herbal drug delivery systems for the neuroprotective effect.

Keywords: herbal, novel drug delivery system (NDDS), neurodgeneration

1. Introduction
In the past few decades, considerable attention has been focused on the development of a novel drug delivery system for drugs. Herbal drugs are becoming more popular in the modern world with less toxic effects and better therapeutic effects. Novel herbal drugs cure specific diseases by targeting the affected region and transporting the drug to that area. Novel drug delivery system is advantageous in delivering the herbal drug at a prearranged rate at the site of action which minimizes the toxic effects and increases the bioavailability of drugs.

In novel drug delivery technology, control of drug distribution is achieved by a carrier system or by changing the structure of the drug at a molecular level. Incorporation of herbal drugs in the delivery system also increase solubility, enhanced stability, protection from toxicity, enhanced pharmacological activity, and protection from physical and chemical degradation. For example, liposomes act as potential vehicles to carry anti-cancer agents by increasing the number of drugs in tumor area and decrease the exposure or accumulation of the drug in normal cells or tissues thereby preventing tissue toxicity. The phytosomal carriers have been studied for the effective delivery of herbal extracts of ginseng. Direct binding of phosphatidylcholine to herbal extract components led to better absorption characteristics as compared to conventional delivery of herbal extracts. Other vesicular assemblies like microspheres, nanoemulsions, polymeric nanoparticles, etc. have been proved beneficial to carry herbal components (Bhokare *et al*., 2016) [9].

However, modern phytopharmaceutical research can solve the scientific needs (such as determination of Pharmacokinetics, mechanism of action, site of action, the accurate dose required, etc.) of herbal medicines to be incorporated in novel drug delivery system, such as nanoparticles, microemulsions, matrix systems, solid dispersions, liposomes, solid lipid nanoparticles. Various drug delivery and drug targeting systems are currently under development to minimize drug degradation and loss, to prevent harmful side effects (Kumar *et al*., 2012; Kharat *et al*., 2014) [8, 23]. An extensive research is going on in the area of novel drug delivery and targeting for plant constituents. However, research in this area is still at the exploratory stage. Hence, there is a great potential in development of novel drug delivery system for valuable herbal drugs. The present review consider the association between NDDS and neurodegeneration by focusing on various approaches and principal mechanisms of herbal constructed drug delivery to the target site in the brain.

2. Neurodegenerative disease
Neurodegenerative diseases occur when nerve cells in the brain or peripheral nervous system lose function over time and ultimately die (Pizza *et al*., 2011) [35]. Although treatments may help relieve some of the physical or mental symptoms associated with neurodegenerative diseases. However, various neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis and psychiatric disorders affect millions of people worldwide. Although Alzheimer's disease and Parkinson's disease are the most common types, the pathogenesis of many of these diseases remains unknown (Brown *et al*., 2005) [11].

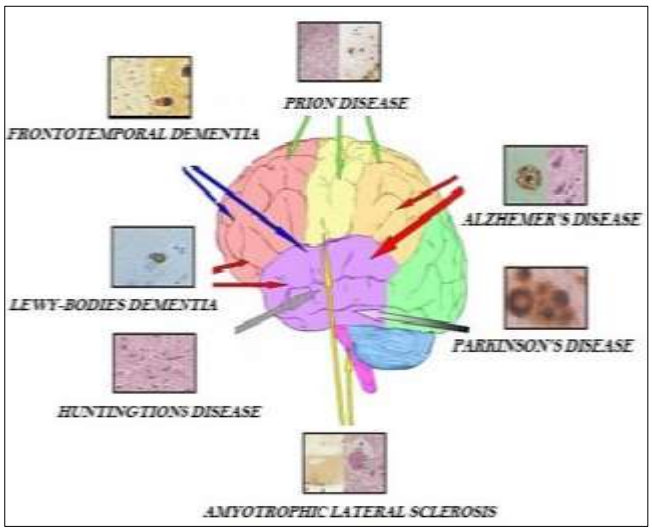


Fig 1

3. Herbal drugs in Neurodegenerative diseases

Ashwagandha is used extensively in Ayurveda as a nervine tonic, aphrodisiac, and adaptogen and helps the body adapt to stress (Mishra *et al*., 2000; Wollen 2010) [4, 52]. It is categorized as a Rasayana (rejuvenating) and is believed to possess antioxidant activity, free radical scavenging activity with an ability to support a healthy immune system (Russo *et al*., 2001) [36].

Turmeric (Zingiberaceae) is a rhizomatous herbaceous perennial plant of the ginger derived from the rhizome and root. The active constituents are thought to be turmerone oil and water-soluble curcuminoids, including curcumin (Aggarwal *et al*., 2007) [1]. Curcumin is the principal curcuminoid and is responsible for the yellow color of the turmeric root (Aggarwal *et al*., 2007; Shishodia *et al*., 2005; Begum *et al*., 2008) [1, 43]. Shankapushpi including Convolvulus pluricaulis, Convolvulus microphyllus, Evolvulus alsinoides, and Clitoria ternatea have been studied. The whole part of Shankhpushpi is used in various formulae as a nervine tonic for the improvement of memory and cognitive function (Bihaqi *et al*., 2009; Malik *et al*., 2011) [10, 28].

Centella Asiatica is one of the important rejuvenating herbs for nerve and brain cells and is believed to be capable of increasing intelligence, longevity, and memory (Shinomol *et al*., 2011) [42]. Centella Asiatica showed antioxidant activity in Alzheimer's disease by reducing brain regional lipid peroxidation and protein carbonyl levels, therefore, protection of DNA damage occur (Tiwari *et al*., 2011) [10].

Jyotishmati (Celastrus paniculatus) is a treasured medicinal herb that is for its effects on the brain has been used for sharpening the memory and improving concentration and cognitive function (Bhanumathy *et al*., 2010) [7]. Formulation of some Indian medicinal plants classified in Ayurveda, the classic Indian system of medicine as drugs considerably ameliorate memory and intellect. (Bhattacharya *et al*., 1997, Kumar 2006) [8]. Studies on rats demonstrated that the oral administration of Trasina herbal formulation once daily for 21 days reduced frontal, cortical and hippocampal acetylcholine (ACh) concentrations, choline acetyltransferase (CAT) activity and muscarinic cholinergic receptor binding (Bhattacharya *et al*., 1997) [8].

It is also examined by various researchers that Bacopa monniera, a traditional The ayurvedic plant is used for centuries as a memory-enhancing, anti-inflammatory, analgesic, antipyretic, sedative and antiepileptic agent (Shikha *et al*., 2009) [41]. Moreover, Bacopa monniera extract was able to reverse both anterograde and retrograde amnesia induced by Scopolamine (Saraf *et al*., 2011) [3]. Bacopa monnieri extracts also improved the escape latency time ($p<.01$). These findings suggest that Bacopa monnieri is a potential cognitive enhancer and neuroprotectant against Alzheimer's disease (Uabundit *et al*., 2010) [49].

It has been lately observed that alcoholic extract of Bacopa monnieri significantly improves escape latency time in Morris water maze test (Uabundit *et al*., 2010) [50]. Bacopa monneri showed antioxidant activity in Alzheimer's disease by increasing the levels of superoxide dismutase, catalase and glutathione peroxidase in the prefrontal cortex, striatum, and hippocampus (Stough *et al*., 2001) [46].

Anwala churna (Emblica officinalis Gaertn) showed exemplary improvement in memory and brain cholinesterase activity (Vasudevan *et al*., 2007) [51]. Ocimum sanctum showed antioxidant activity in Alzheimer's disease by inhibiting the lipid peroxide generation (Gupta *et al*., 2012) [18]. Withania somnifera showed antioxidant activity in Alzheimer's disease by increasing the levels of the major free radical scavenging enzymes like superoxide dismutase, catalase and glutathione peroxidase in the frontal cortex and striatum (Barbosa *et al*., 2006; Mirjalili *et al*., 2009) [5, 29]. Withania somnifera improved memory deficits in mice with a model of Alzheimer's disease induced by the amyloid peptide. (Tohda *et al*., 2009) [48].

Brahmi rasayana significantly improved learning and memory in young mice and reversed the amnesia induced by both scopolamine and natural aging. The extract significantly decreased whole brain acetyl cholinesterase activity (Joshi *et al*., 2006) [22]. It was also investigated that hydroalcohol extract from Centella asiatica, Nardostachys jatamansi, Myristica fragrans, Evalvulus alsinoides inhibited 50% of AChE activity at concentrations of 100-150µg/mL (Mukherjee *et al*., 2007) [31].

4. Types of novel drug delivery systems

4.1. Liposomes

A liposome has an aqueous solution core surrounded by a hydrophobic membrane, in the form of a lipid bilayer; hydrophilic solutes dissolved in the core cannot readily pass through the bilayer. Hydrophobic chemicals associate with the bilayer. The liposome can be hence loaded with hydrophobic and/or hydrophilic molecules. To deliver the molecules to a site of action, the lipid bilayer can fuse with other bilayers such as the cell membrane, thus delivering the liposome contents; this is a complex and non-spontaneous event (Cevc and Rcihardsen 1993).

4.2. Nanoparticle

Nanoparticles for the purpose of drug delivery are defined as submicron colloidal particles. It includes monolithic nanoparticles in which the drug is dissolved, or dispersed throughout the matrix and nanocapsules (Kreuter 2004) [24]. Nanoparticles are made from biocompatible and biodegradable materials such as polymers, either natural (e.g., gelatin, albumin) or synthetic (e.g., polylactides, polyalkylcyanoacrylates), or solid lipids. These drugs cross the blood-brain barrier (BBB) and deliver pharmaceuticals to the brain for therapeutic treatment of neurological disorders. These disorders include Parkinson's disease, Alzheimer's

disease, schizophrenia, depression, and brain tumors.

4.3. Microemulsion

Microemulsions are clear, stable, isotropic mixtures of oil, water, and surfactant, frequently in combination with a co-surfactant. These systems have considerable potential to act as drug delivery vehicles by incorporating a drug molecule (Lawrence and Rees 2000) [27]. However, micro-emulsion can deliver drug molecules through a diverse range of routes of administration like oral, nasal, parenteral, pulmonary, and ocular delivery. Recently there is a significant increase in the number of scientific articles describing the use of micro-emulsion for drug delivery to the brain. (Lawrence *et al*., 2000) [27].

4.4. Phytosomes

Phytosomes are little cell-like structures. This is an advanced form of herbal formulations that contain the bioactive phytoconstituents of herb extract surrounded and bound by a lipid. Most of the bioactive constituents of phytomedicines are water-soluble compounds like flavonoids, glycosides, terpenoids, etc out of which flavonoids are a major class of bioactive compounds that possesses broad therapeutic activities. As they are water-soluble, phytosomes protect valuable component of herbal extract from destruction by digestive secretion and gut bacteria (Jain *et al*., 2010) [21]. Solubility (i.e. hydrophilic or lipophilic) is an important criterion for the development of novel formulations. (Pawar and Bhangale 2015) [34]. In addition, an appropriate type of dosage form for delivery of phytosomes can be selected based on its potential for improving the effectiveness and efficiency of bioactive compounds. Phytosome technology has been effectively used to enhance the bioavailability of many popular herbal extracts like milk thistle, grape seed, green tea, ginseng, etc.

4.5. Transdermal drug delivery system

Transdermal Drug Delivery Systems are defined as self-contained, self-discrete dosage forms which when applied to the intact skin, delivers the drug at a controlled rate to the systemic circulation. A simple patch that can stick on to the skin like an adhesive bandage facilitate passive diffusion of drugs across the skin as the delivery mechanism (Garala *et al*., 2009) [15]. Transdermal delivery system provides the advantage of controlled drug delivery, enhanced bioavailability, reduction in side effects and easy application. Transdermal formulation of boswellic acid and curcumin has been developed for continuous drug administration (Goyal *et al*., 2011) [17].

4.6. Ethosomes

Ethosomes are vesicular carrier comprising of hydroalcoholic phospholipid in which the concentration of alcohols is relatively high. To provide continuous drug infusion through an intact skin, several transdermal therapeutic systems have been developed for topical application (Patrekar *et al*., 2015) [33]. Ethosomes are too small to be detected by immune system and moreover they can be used to deliver the drug in the target organ. Ethosomes comprise of phospho-bilipid layers along with ethanol which gives efficient permeation and penetration of the drugs and deliver large molecules such as peptides, protein molecules (Singh *et al*., 2015) [10]. Moreover, ethosomes open new challenge and opportunities for the development of novel improved therapies. Transdermal route is a promising alternative to drug delivery for systemic effect. Ethosomes have initiated a new area in vesicular research for transdermal drug delivery which can provide better skin permeation than liposomes. Application of ethosomes provides the advantages such as improved permeation through skin and targeting to skin layers for skin diseases.

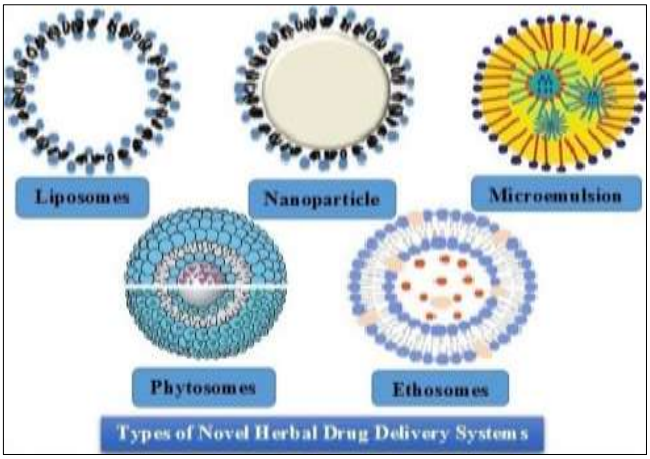


Fig 2

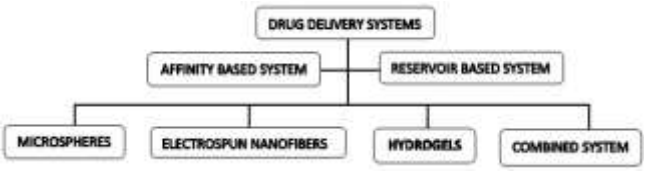
5. CNS based drug delivery

Successful treatments for neurodegenerative disorders (NDs) have been limited and drug delivery to the brain remains one of the major challenges. There has recently been growing interest in the development of drug delivery systems (DDS) for local or systemic brain administration. Drug delivery systems are able to improve the pharmacological and therapeutic properties of conventional drugs and reduce their side effects (Garbayo *et al*., 2012) [16]. Due to the limited effectiveness of available treatments in halting the neurodegenerative process, new therapies are under research like therapies based on growth factors. However, the efficacy of these new treatments depends not only on the application of neurotrophins but also on the approaches used to deliver (Herran at al., 2014) [20].

Various strategies like non-invasive methods, including drug manipulation encompassing transformation into lipophilic analogs, prodrugs, chemical drug delivery, and carrier-mediated drug delivery, receptor-mediated drug delivery, and intranasal drug delivery, etc. adventures the neuronal pathways to deliver drugs to the brain. In addition, the invasive methods mainly depend on the disruption of the blood-brain barrier (BBB) or direct intracranial drug delivery by intracerebral administration (Pathan *et al*., 2009) [32]. The use of nanoparticle formulations are able to encapsulate molecules with therapeutic value. Targeting specific transport processes in the brain vasculature may enhance drug transport through the BBB in neurodegenerative disorders and target relevant regions in the brain (Saraiva *et al*., 2016) [39].

Nanotechnologies include polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, microemulsion, nanoemulsion, and liquid crystals and these are specific tools for the delivery of therapeutic devices to the brain (Fonseca *et al*., 2015) [14]. However, liposomes, nanoparticles, nanocapsules, nanoemulsions, microspheres are some of the novel herbal formulations. Novel drug delivery systems for herbal medicines have a potential future which may be helpful to target the various neurodegenerative

complications and overcome the central nervous system associated problems. They may enhance their bioavailability and safeguards the sustained drug delivery for neurodegenerative disorders (Ajazuddin and Saraf 2010) [3].



6. Herbal drug and novel drug delivery systems

Phytotherapeutics need a scientific approach to deliver the components in a sustained manner to increase patient compliance and avoid repeated administration. This can be achieved by designing NDDSs for herbal constituents (Singh *et al*., 2011) [10]. Nanocarriers applying to herbal remedies carry an optimum amount of the drug to their site of action bypassing all the barriers. Hence, the use of herbal remedies through NDDS may enhance the efficacy of herbal remedies (Yadav *et al*., 2011; Bairwa *et al*., 2010) [53, 4].

Liposomes i.e. hydrophilic and lipophilic are composed of natural or synthetic phospholipids, which consist of concentric bi-layered vesicles in which aqueous volume is entirely enclosed by a membranous lipid bi-layer and therefore liposome as a drug carrier can indiscriminately deliver drugs through the cell membrane. (Gupta *et al*., 2012) [21]. Liposomes being highly lipophilic can cross the blood-brain barrier (BBB) and deliver the loaded extract to the brain successfully. Hence, extract loaded liposomes would be the ideal dosage form for the treatment of numerous neurodegenerative diseases. (Chaturvedi *et al*., 2011) [13].

7. Novel drug delivery systems and neuroprotective drugs

Increasing knowledge of the neurochemical aspects of central nervous system function raises the possibility of treating Alzheimer's disease (AD) and other neurological diseases by the appropriate manipulation of neurotransmitters, neuromodulators, neurohormones or neurotrophic factors. Novel CNS-directed drug delivery systems might be used to overcome CNS related problems. (Harbaugh *et al*., 1989) [19]. Conventional treatment strategies such as acetylcholinesterase inhibitor drugs in Alzheimer's disease often fail due to their poor solubility, lower bioavailability, and ineffective ability to cross the blood-brain barrier (BBB). Therefore, nano-technological treatment methods which involve the design, characterization, production, and application of nanoscale drug delivery systems has been employed to optimize therapeutics. These nanotechnologies include polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, microemulsion, nanoemulsion, and liquid crystals which may be helpful to target CNS related diseases. (Santos *et al*., 2015) [14].

Treatment strategies for the neurodegenerative disease are still elusive. Available pieces of evidence suggest that in AD, passage across the blood-brain barrier (BBB) and transport exchanges for amyloid-β-peptide between blood and the central nervous system compartments play an important regulatory role in the deposition of the brain. On the other hand increased BBB permeability in AD is also likely since structural damage of endothelial cells is quite frequent in the AD brain. Thus, enhanced drug delivery in AD is needed to induce neuroprotection and therapeutic success. For this purpose, nano-drug delivery could be one of the available options that require active consideration for novel therapeutic strategies as a neuroprotective (Sharma *et al*., 2012) [10].

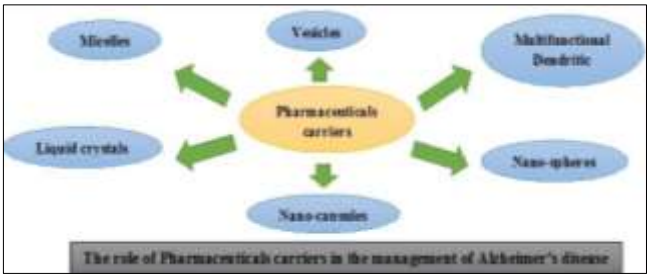


Fig 3

8. Conclusion

Herbal medicines have been widely used all over the world since ancient times and have been recognized by physicians and patients for their better therapeutic value as they have fewer adverse effects as compared with modern medicines. The drugs of ayurvedic origin can be utilized in a better form with enhanced efficacy by incorporating in modern dosage forms. However, phytotherapeutics need a scientific approach to deliver the components in a novel manner to increase patient compliance and avoid repeated administration. This can be achieved by designing novel drug delivery systems for herbal constituents. On the basis of above discussion it can be concluded that herbal novel drug delivery systems including various phytosomes, nanoparticles, microsomes, liposomes, and ethosome may help the pharmaceutical and herbal industry for the development of a new formulation for the treatment of neurodegenerative disorders and may open a new door to the researchers working in the field of central nervous system-related other difficulties to target the specific site in the brain.

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