

# Role of medicinal plants in neurodegenerative diseases

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Received: 5 December 2015 / Accepted: 20 June 2017 / Published online: 24 October 2017  
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**Abstract** Neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD), are characterized by progressive loss (and even death) of structure and function of neurons, and have created great burden to the individual and the society. The actual cause of various neurodegenerative diseases still remains a mystery in healthcare. Some of the commonly studied environmental factors causes for neurodegenerative diseases are protein degradation, oxidative stress, inflammation, environmental factor, mitochondrial defects, familial history, and abnormal protein accumulation in neuron. However ageing plays a very important role in neurodegenerative diseases. Medicinal plants and natural compounds, such as *Withania somnifera* (ashwagandha), *Ginseng*, curcumin, resveratrol, *Baccopa monnieri*, *Ginkgo biloba*, and Wolfberry have been applied to prevent or alleviate neurological diseases and relief of neurological symptoms reported in in vivo or in clinical trails. Natural compounds in nanosize range as a therapeutic agent

possess the same activity as in native state. Nanodrug delivery helps to increase the bioavailability of the drug and thereby specifically target cells and tissues. Nanoparticles, polymeric nanomicelles, complex polymers nanocrystal, and nanofibers are used to carry the medicinal plants for drug delivery system in the treatment of neurodegenerative diseases. Especially, electrospinning and electrospraying as straightforward yet versatile techniques for the production of nanosized fibers and particles possess huge potential in encapsulation of natural compounds for the neurodegenerative diseases. This review is a study to understand the role of nanotechnology and natural compounds in neurodegenerative diseases associated with ageing.

**Keywords** Ageing · Electrospinning · Electrospraying · Neurodegenerative disease · Natural compounds · Nanoformulation

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## Introduction

Millions of people worldwide are affected with neurodegenerative diseases every year. The number of people affected by Alzheimer's disease alone increased from 26.6 million in the year 2006 to 36 million in the year 2014, out of which 5.1 million are Americans of all ages, of which 200,000 are under age 65 (younger-onset Alzheimer's) [107]. The cost for neurodegenerative disease treatment is very high; more than \$100 billion is spent every year for Alzheimer's disease [23, 86]. Neurodegenerative diseases are characterized by the progressive damage and dysfunction of the neurons or the nerve cells. Neurodegenerative disease causes regarding protein degradation [101], various environmental factors [23], mitochondrial defects, familial

history [15, 89], abnormal protein accumulation in neurons etc. [11]; however aging is considered as one of the major problem in neurodegenerative diseases [59].

Over the past few decades, a large number of advanced technologies have been developed in order to specifically carry huge number of different compounds and bioactive molecules to mitochondria. These technologies has allowed a significant step forward in terms of improvement of drug pharmacokinetic profile, intracellular penetration, distribution at the target site, and improvement of the pharmacological effects [34]. Specific attention has been given to the development of useful drug delivery systems consisting in nano-sized materials (1–100 nm) which has the ability to cross several biological barriers, to protect the drugs from premature deactivation thereby improving their pharmacokinetic profile, and also to increase the internalization and distribution of the molecules of interest at the target site [48]. Many efforts have been made in order to propose nano-drug delivery systems, which possess these specific characteristics. Despite several promising findings in nano-drug delivery systems represents still new research area required for further extensive investigations and analysis.

Herbal medicines *Ginseng*, *Ashwagandha*, *Baccopa monnieri*, *Ginkgo biloba*, *Centella asiatica*, and compounds such as flavonoids, celastrol, trehalose, lycopene, sesamol, resveratrol, and curcumin has gained a lot of interest for their therapeutic potential. Table 1 summarizes some of the commonly used natural compounds for their neuroprotective effect. However, the use of such natural compounds and their derivatives in the nanoscale size range for the treatment of neurodegenerative diseases remains a challenge due to various reasons such as extraction, nanomanufacturing technique, route of administration, toxicity etc. [122, 129] (Fig. 1).

Parkinson's disease (PD) mainly affects the motor system of the brain. The death/dysfunction of dopamine generating cells are the root cause for the disease. A cascade of events lead to the outbreak of the disease; namely oxidative stress, mitochondrial dysfunction, misfolding during protein synthesis, excitotoxicity by various biochemical pathway (glutamate pathway), lysosome impairment and autophagy by chaperone and the formation of Lewy bodies due to protein misfolding takes place which lead to disease condition. Lewy bodies are made up of neurofilament protein and ubiquitinated  $\alpha$ -synuclein (Fig. 2). Braak's staging illustrates that the lewy bodies are usually found in the olfactory region and in the lower region of the brain stem; but as the disease progresses the Lewy bodies reach the substantia nigra of midbrain and forebrain; and in advance stage it reaches the neocortex region of the brain. A study by Hughes et al. [58] revealed that certain neuronal undergo a field change due to widespread lewy body distribution. They suggest that a field

change is commonly observed in tyrosin hydroxylase synthesizing cells. Among the big list of neurodegenerative diseases such as Acute disseminated encephalomyelitis, Creutzfeldt–Jakob disease, Epilepsy and Epileptic syndrome, Gerstmann–Straussler–Scheinker disease, Juvenile neuronal ceroid lipofuscinoses, Kuru (prion disease), Leukodystrophies, Machado–Joseph disease, Multiple sclerosis, neurodegeneration in Diabetes Mellitus, Neurofibromatoses, Pick's disease, Tourette syndrome.; Parkinson's, Huntington and Alzheimer's disease are associated with aging and are widely studied over the past few decades [40, 60].

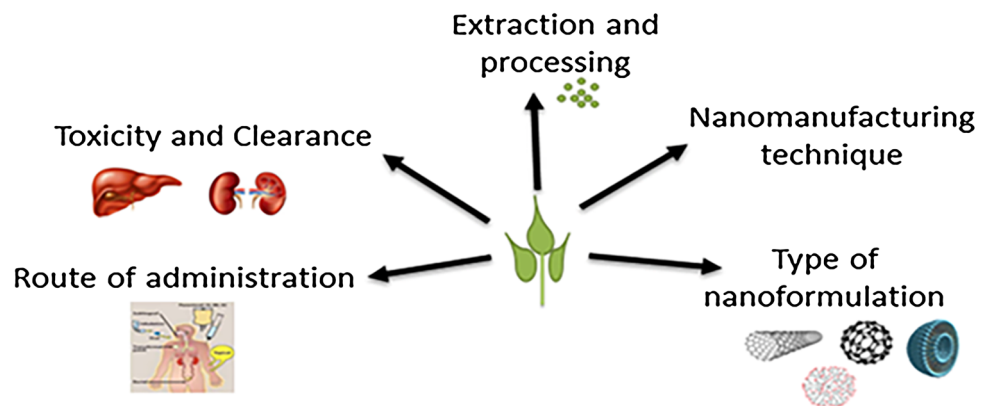
Similar to Parkinson's disease, another commonly found neurodegenerative disease in the elderly is Alzheimer's disease (AD). Age is a major risk factor for neurodegenerative disease as the person slowly losses the ability of self-repair. Alzheimer's disease can be classified as familial/genetic and sporadic AD. In genetic/familial AD disease condition starts at a very young age; on the other hand sporadic AD occurs in elderly person. The disease is an outcome of mutation in amyloid precursor protein (Fig. 2). Moreover, plaque and neurofibrillary tangle formation containing  $\beta$ -amyloid and phosphorylated tau proteins are some of the pathological condition in the disease.  $\beta$ -amyloid proteins are made up of 39–42 amino acid residues, extracellular and transmembrane domains of APP (amyloid precursor protein) are the source of origin of  $\beta$ -amyloid. The key factor associated with sporadic AD is the cleavage of APP by  $\beta$  and  $\gamma$  secretases which leads to the formation of 4 kDa  $A\beta$  peptide. Hebert et al. [51] investigated the change in microRNA expression and observed that miRNA are involved in APP regulation and there was a decrease in BACE1 expression in sporadic disease condition. The study also suggests that the increase in BACE1 and  $A\beta$  level is due to the loss of specific miRNAs.

Huntington's disease (HD) named after George Huntington is said to be caused by genetic mutation in the genes of chromosome 4. The disease is characterized by moment disorder generally occurs in the fourth or fifth decade of a person's life and tend to progress for 10–20 years later. The disease rarely found in juveniles, where the symptoms are more severe including rigidity [84]. This autosomal disease is an outcome of elongated CAG (cytosine, adenine, and guanine) repeat (Fig. 2); the onset of the disease thus depends on the length of the CAG repeat. Huntingtin a mutant protein results from CAG repeats, this in turn leads to polyglutamic strand at the N-terminus [79]. The symptoms vary among individual, however mental instability/behavioral abnormality is one of the common symptom of Huntington's disease. A recent study indicated that  $Ca^{2+}$  loading in mitochondria is drastically high in HD cells even under resting state. This high  $Ca^{2+}$  loading is the root cause of mitochondrial DNA damage which further leads

**Table 1** Natural compounds with neuroprotective effect

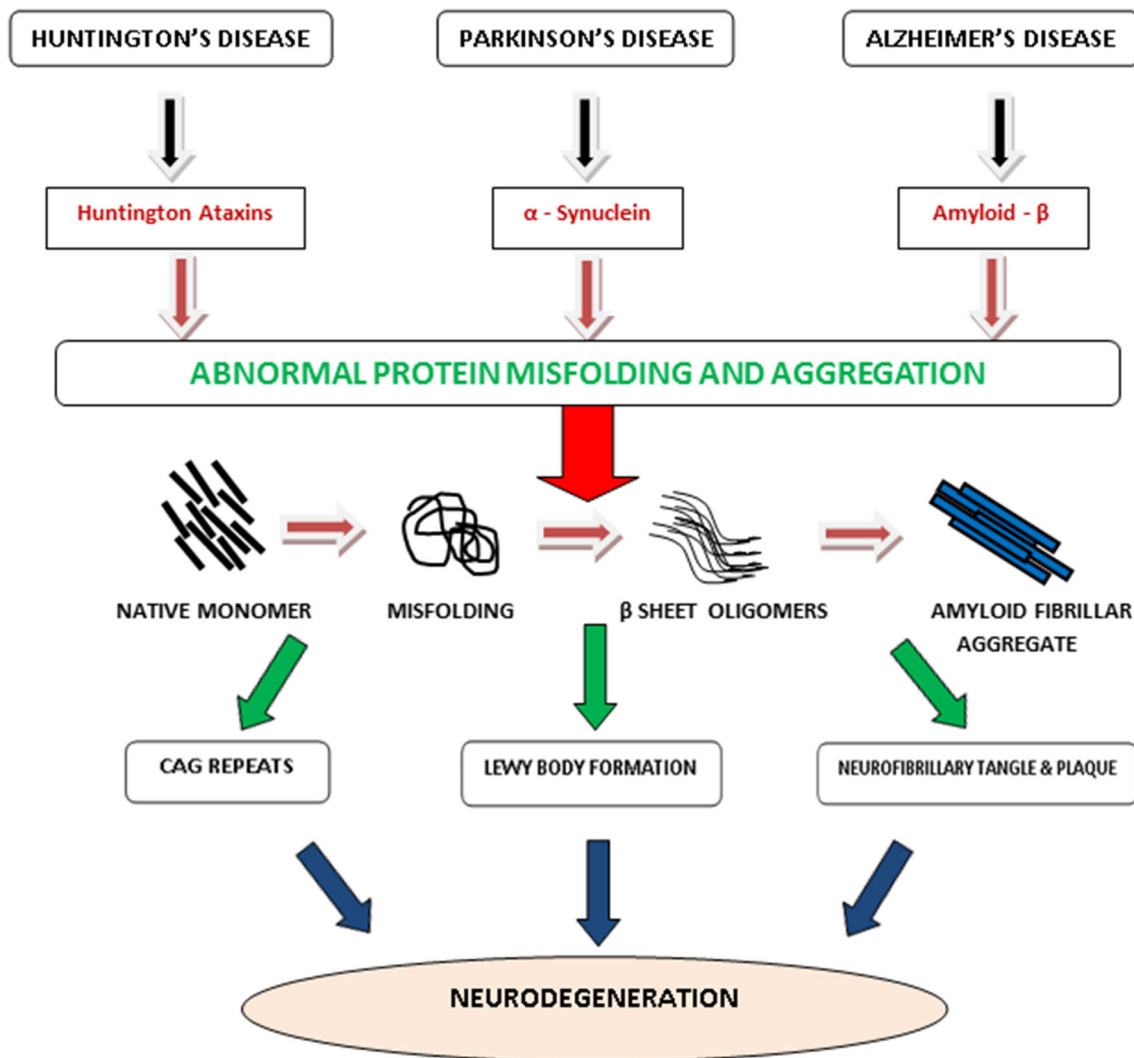
Agent	Active ingredient	Animal Model	Route of administration	Activity	References
<i>Centella asiatica</i> extract (Known as Gotu kola)	Asiaticoside, madecassoside, asiatic and madecassic acids	Sprague–Dawley rats	Intravenous and oral	Inhibit the 3-NP induced depletion Protects against mitochondrial dysfunction induced by 3-NP	[30, 112]
Flavonoids		Rats	Oral	Inhibit nitric oxide synthase	[30, 82]
Naringin		Rabbit	Intravenous	Scaveng ROS & reactive nitrogen species	
Hesperidin		Mice	Intraperitoneal/ oral		
Kaempferol					
EGCG					
Celastrol ( <i>Tripterygium wilfordii</i> )	Triptolide	Mice	Oral	Inhibit pro-inflammatory cytokines production, NO synthase peroxidation of lipid Ability to attenuate loss of dopaminergic neurons & dopamine depletion	[4, 30]
Trehalose (a non-reducing disaccharide)	Trehalose	Mice, rat	Intravenous and oral	Inhibition of $\beta$ amyloid, protein aggregation mediated by polyglutamine (poly Q) <sup>3</sup> Increased autophagic activity	[30, 81, 104]
Lycopene (Present in tomatoes)	Lycopene	Mice, pig	Oral	Attenuate biochemical changes induced by 3-NP	[30, 75, 103]
Sesamum indicum Linn (sesame)	Sesamol	Mice	Intravenous	Protect against neuroinflammation in hippocampus neurons Improve synaptic plasticity and neurotransmission	[56] [30]
Coffee beans extracts	Caffeine	Mice, Wistar rats	intrastratial injection	Helps in modulating adenosine A <sub>2A</sub> receptors in brain Attenuate dopaminergic neurotoxicity	[100]
<i>Convolvulus pluricaulis</i> extract	<i>Convolvulus pluricaulis</i>	Rats	Oral	Inhibits the enzymatic activity of acetylcholine esterase Helps in maintaining the level of various mRNA receptors such as M1 receptors, nerve growth-factor tyrosine kinase A receptor, choline acetyl transferase	[21]

**Fig. 1** Challenges in the use of natural compounds in the nanosize range



to mitochondrial dysfunction in HD cells [133]. Neuro-pathogenesis of Huntington’s disease is characterized by atrophy of various regions in the brain such as the caudate nucleus, putamen, and segments of globus pallidus in the

initial stage; as the disease progresses the atrophy occurs in the regions such as cerebellum, cerebral cortex, thalamus, and cerebral white matter [130]. Moreover, other issues like oxidative stress, dysfunction in metabolic activity and



**Fig. 2** Molecular pathogenesis in neurodegenerative diseases. Carlo et al. [25] Modified from [short citation]. (© 2011 Di Carlo M, Picone P, Carrota R, Giacomazza D, San Biagio PL. Published under CC BY 3.0 license)

genetic mutation are also said to be responsible for neuronal damages and cell death.

### Medicinal plants and natural compounds commonly used for neurodegenerative diseases

#### *Withania somnifera* (ashwagandha)

*Withania somnifera* also known as Ashwagandha is an Ayurvedic medicine which has been used for many decades for its anti-inflammatory, anti-oxidant [20], anti-stress and neuroprotection [61], immune boosting and memory power enhancing ability [70]. Raut et al. [99] studied on *W. somnifera* to evaluate dose related tolerance, safety and activity and suggested that the average tolerance dose concentration was 750–1250 mg/day. The extract also

possesses muscle strengthening and lipid lowering ability. The various Withanolides compounds of Ashwagandha was proven for its anti-proliferative activity in lung, central nervous system and breast cancer cell lines, moreover *Withanolides* when included in diet is said to inhibit tumor growth [63]. *Withania somnifera* inhibited NADPH-d activity which is induced by stress, the mode of action of *W. somnifera* on NADPH-d by inhibiting the release of corticosterone and by activating cholineacetyltransferase which boost serotonin in hippocampus [18]. The active components of *W. somnifera* such as withanolide A (first isolated withanolide from *W. somnifera*), withanolide IV, withanolide VI possess the ability of reconstructing the pre-synapses and post-synapses; and also involves in the regeneration of neuronal axons and dendrites. Many plant species are been used for treating various ailments in humans, the use of extract either as crude or semi-purified

form is proved for its therapeutic effect [24]. Bhattacharya and Muruganandam [19] demonstrated the anti-stress activity of *W. somnifera* extracts treated on Wistar rats and the chronic stress which induced perturbations were inhibited by *W. somnifera*.

### Ginseng

*Ginseng*/panax inseng is a medicinal herb of Korean and Chinese origin. This herb is known for its medicinal properties for many years. The herb is used for treating diseases such as cancer, neurodegenerative disorder, hypertension and diabetes. *Ginseng* is also reported for its immune boosting ability and thereby resists illness. Nah et al. [90] studied on *Ginseng* which has the ability to inhibit voltage dependent  $Ca^{2+}$  channels by a receptor linked to G protein which is sensitive to toxin. The study revealed that *Ginsenoside* a saponin which is found in trace amount helps in modulating neuronal  $Ca^{2+}$  channels. Researchers have investigated on the immune modulatory effect of *Ginseng* [67]. The inhibitory activity of a metabolite of *Ginseng* (compound K) is to be more potent than commercial anti-allergic drugs [29]. The *Ginsenosides* (Rb<sub>1</sub> and Rg<sub>3</sub>) of *Ginseng* possess neuroprotective effect thereby making them an excellent compound for treating neurodegenerative diseases [73]. The active compound of *P.ginseng*, is proven for its neuroprotective effect on dopaminergic neurons by inhibiting the elevation of nigral iron level, lowering the expression of DMT1 (divalent metal transporter) and potentially increasing the expression of FP1 (ferroportin) in Parkinson's disease [132]. Chen et al. [27] suggested that Rg<sub>1</sub> reduces the ROS (reactive oxygen species) production by dopamine, release of cytochrome c into the cytosol, inhibition of caspase 3 activity, and lowers the NO production by reducing the inducible nitric oxide (NO) synthase protein level. Rg<sub>1</sub> is also reported for its activity in reducing cell injury by hydrogen peroxide by down-regulating NF- $\kappa$ B signaling pathway and activation of Akt and ERK [80].

### Curcumin

Curcumin or turmeric a commonly used spice in India is known for its cosmetic and medical properties in Ayurveda for many years. The spice is basically a store house of dietary fiber, potassium, magnesium, iron and vitamins. The medical properties of the herb are diverse, some of which include anti-inflammatory, anti-oxidant and it has a high potential in boosting the immune response. Curcumin plays a prominent role in down regulating certain transcription factors, enzymes and cytokines [2, 148].

Mode of action of curcumin in Alzheimer's disease is by boosting the macrophages. Studies reveal that curcumin helps the macrophage in clearing off the amyloid plaque which is formed in AD. Zhang et al. [146] demonstrated the role of curcumin in clearing amyloid plaque by treating the macrophages of AD patients with curcumin and later introducing it with amyloid plaque. The result proved that macrophage treated with curcumin had a greater uptake and ingestion of plaque in comparison with non treated macrophages. Various studies reveal that anti-inflammatory property of curcumin and also have a potent role in preventing A $\beta$  oligomer and fibril formation [92, 141]. Curcumin is useful in the regulation of the cerebral microcirculatory function and hypertension. Xia et al. [139] investigate the therapeutic effect of curcumin on hypertension and its putative mechanisms in the cerebral microcirculation. Curcumin treated mice showed reduced blood pressure compared to the irrespective controls. It helped to increase blood velocity and LDF flow in hypertensive and normotensive rats, it also altered the circulating endothelial cells and open capillaries. These research groups suggests that the curcumin exerts its therapeutic effect in male albino rats by regulating vasomotion function, increasing blood perfusion, releasing the peripheral resistance and opening efficiently capillaries. Curcumin is a potent compound acting against the depression in the male albino rats, Chang et al. [26] studied that curcumin significantly reduced olfactory bulbectomy-induced behavioural abnormalities including deficits instep-down passive avoidance, increased activity in the open area and immobility time. Chronic administration of curcumin reversed the levels of 3,4-dihydroxyphenylacetic acid, noradrenaline, serotonin and 5-hydroxyindoleacetic acid in the hippocampus region of male albino rats. Curcumin helps to normalize the levels of dopamine, noradrenaline, and 5-hydroxyindoleacetic acid in the frontal cortex of rats. Baum et al. [14] conducted 6-month randomized, placebo-controlled, double-blind pilot clinical trial of curcumin in patients with Alzheimer Disease. 22 patients randomized to 4 or 1 g, 10 patients chosen to take curcumin/placebo as 10 capsules to swallow after a meal; and 12 patients, as a packet of powder to mix with food. It was observed that curcumin raised vitamin E, the antioxidant activity of curcuminoids decreased the need for and depletion of the antioxidant vitamin E. It was also observed that curcumin slows AD progression. The serum A[ $\beta$ ]<sub>40</sub> levels did not differ significantly among doses, serum A[ $\beta$ ]<sub>40</sub> tended to rise on curcumin, reflecting on the ability of curcumin to disaggregate A[ $\beta$ ] deposits in the brain, releasing the A[ $\beta$ ] for circulation and disposal. It was also observed that curcumin did not seem to cause side effects in AD patients (rather, there was a tendency toward fewer adverse events on 4 g).



## Resveratrol

Resveratrol (3,4',5-trihydroxystilbene), is a type of natural phenol; grape, raspberries, blue berries and mulberries are the rich source of Resveratrol. This polyphenolic compound has multiple beneficial effect in disease such as cardiovascular [94, 128], Alzheimer's disease [6]. Feng et al. [42] studied the effect of immune modulation at low dose of Resveratrol administration and suggested that low dose of Resveratrol lead to the enhancement of cell-mediated immune response by inducing the production of cytokine and by influencing macrophage function. Kim et al. [72] investigated the ability of Resveratrol in protecting the neurons from  $\beta$ -amyloid induced cell death.

The active compound Piceatannol (monohydroxylated derivative) in Resveratrol is said to block the accumulation of ROS induced by A $\beta$ . Resveratrol has also been proven for its anti-inflammatory effect. Studies prove that compounds such as Tyrosol and Caffeic acid of Resveratrol inhibit the effect of tumor necrosis factor  $\alpha$ , interleukin-1 $\beta$  and interleukin 6 productions [16, 17]. Dasgupta and Milbrandt [36] demonstrated the neuroprotective effect of Resveratrol, in which Resveratrol helps in stimulating AMP kinase and thereby affect neuronal homeostasis. Wang et al. [131] proved that combined treatment with Mouse bone marrow mesenchymal stem cells (mBM-MSCs) and Resveratrol enhanced the immunomodulatory effects, suppressed proinflammatory cytokines (IFN- $\gamma$ , TNF- $\alpha$ ) and increased anti-inflammatory cytokines (IL-4, IL-10) in experimental autoimmune encephalitis was induced in C57BL/6 mice. The combination of mBM-MSCs and Resveratrol provides a novel potential experimental protocol for alleviating EAE symptoms. Yu et al. [144] investigated on whether Shh (Sonic hedgehog) pathway mediates Resveratrol to decrease cerebral ischemic injury and improve neurological function after stroke. The study suggests that pretreatment with Resveratrol significantly improved neurological function, decreased the volume of infarct, enhanced vitality, and reduced apoptosis of neurons in vivo and in vitro after stroke. Moreover the expression levels of Shh, patched (Ptc) and Smoothed (Smo) receptors, Gli transcription factors 1 (Gli-1) mRNAs was upregulated and Gli-1 was relocated to the nucleus. Under in vivo and in vitro condition, a Smo inhibitor reversed the effects of Resveratrol. Hence, the overall study suggests that decreased cerebral ischemic injury and improved neurological function by Resveratrol is mediated by the Shh signaling pathway.

## *Baccopa monnieri*

*Baccopa monnieri* otherwise known as Brahmi is well known for its medical properties in Ayurveda. *Baccopa*

*monnieri* is commonly found in India and Australia. It has a potential to rejuvenate nerve cells and also has a great ability in improving memory power. The two saponins of Brahmi are Bacoside A and B which are made up of Sapogenins—Bacogenins A<sub>1</sub>–A<sub>4</sub>, Betulic acid and various alkaloids. Among the two main saponins Bacoside A is said to improve the memory power [102]. Apart from memory boosting ability *B. monnieri* is also used as anti-oxidant, anti-stress, anti-inflammatory, anti-microbial and smooth muscle relaxant. Shinomol et al. [111] suggest that the hallmark properties of *B. monnieri* namely anti-oxidant effect and effect against stress mediated dysfunction of nerve cells are key factors for HD treatment. Mishra et al. [87] suggested the availability of GSH (Glutathion) and the activity of GR (Glutathion reductase) play a critical role in *B. monnieri* to fight against oxidative stress caused by metal and the ability to detoxify them. The antistress activity of the saponins (Bacoside A and B) of *B. monnieri* was studied by Chowdhuri et al. [31] in Sprague–Dawley rats. The results suggested that *B. monnieri* has immense ability to activate Hsp70, P450 and superoxide dismutase which thereby help the brain to fight against adverse stress condition.

## *Ginkgo biloba*

*Ginkgo biloba* is an ancient Chinese medicine which is otherwise known as living fossil [44, 49]. The leaf contains various chemical compounds such as trilactonic diterpenes (ginkgolide A-C, ginkgolide J-M), trilactonic sesquiterpene (Bilobalide) and various flavanoids. The leaf extract of *G. biloba* contains active ingredient which is known for its antioxidant properties and it has a potent ability to inhibit aggregation of blood platelets.

This Chinese medicine is also known to improve the cognitive function and blood flow [85]. Yao et al. [142] investigated that the leaf extract of *Ginkgo* has the ability to inhibit the formation of A $\beta$  from  $\beta$  amyloid precursor protein in Alzheimer's disease. It has been reported that the chemical compounds of the extract compete with free cholesterol in order to interact with the A $\beta$  and in turn decrease the aggregation. Neuronal apoptosis which is the root cause for neurodegenerative disease is said to be reduced by *Ginkgo*; moreover it has the ability to inhibit the ROS accumulation by A $\beta$  [13, 41]. Ahlemeyer and Krieglstein [3] suggested that bilobalide in *G. biloba* extract is a potent constituent with neuroprotective and anti-apoptotic activities. Abdou et al. [1] proved that co-administration of *G. biloba* and/or *Trifolium pratense* with sodium arsenite thereby minimized its neurological damages against sodium arsenite-induced neurotoxicity in different parts of brain (Cerebral cortex, Hippocampus, Striatum and Hind brain) and also spinal cord of the rats.

Guo et al. [50] investigated on the neuroprotective mechanism of Ginkgolides or *Ginkgo* flavonoids on the TNF- $\alpha$  induced apoptosis of cultured rat hippocampal neurons. In order to induce apoptosis primary hippocampal neurons isolated from rat brains were cultured with or without addition of Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). TNF- $\alpha$  induced cultures were divided into model group, Ginkgolides pre-treatment group and Ginkgo flavonoids pre-treatment group. The results suggests that Ginkgolides or Ginkgo flavonoids helps in increasing the cell viability and Apoptotic neurons were significantly less in Ginkgolides pre-treatment. The clinical efficacy of the *G. biloba* special extract EGb 761 in dementia of the Alzheimer type and multi-infarct dementia was investigated by Kanowski et al. [68] in which the group studied on the efficacy of the *G. biloba* special extract EGb 761 in outpatients with pre-senile and senile primary degenerative dementia of the Alzheimer type (DAT) and multi-infarct dementia (MID). The study was conducted in a prospective, randomized, double-blind, placebo-controlled, multi-center study. 216 patients received either a daily oral dose of 240 mg EGb 761 or placebo. Clinical efficacy was evaluated by means of responder analysis, with therapy response being defined as response at least in two of the three primary variables. The frequency of therapy response in the treatment group differed significantly in favor of EGb 761, with  $p < 0.005$  in Fisher's Exact Test. The intent-to-treat analysis of 205 patients led to similar efficacy results.

### Wolfberry

Wolfberry/*Lycium barbarum* (LB) is a commonly used Chinese medicine. The medicinal property of the fruit, such as anti-ageing property, is known for many years in Asian countries. Wolfberry is known as "tonic herb" in Chinese medicine because of its anti-ageing potential. The fruit has diverse medicinal properties. Wolfberry is also used for treating diseases such as diabetes and glaucoma. Dried wolfberry fruit is used as a food supplement in recent years. The fruit is made up of water soluble polysaccharides *L. barbarum* which constitute about 40% of wolfberry content [28, 52, 54]. Yu et al. [143] investigated on the neuroprotective activity of *L. barbarum* extract on Alzheimer's diseases [54]. Pretreatment of rat cortical neuron with *L. barbarum* prior to A $\beta$  peptide exposure reduced the lactate dehydrogenase release. The extract also blocked the activity of  $\beta$  amyloid peptide activated caspases-3.

Ho et al. [53] studied on the activity of wolfberry on neural damage induced by plasma homocystein (Hcy). The extract *Lycium barbarum* is said to block the tau phosphorylation which is induced by Hcy, and is also involved in the cleavage of tau. *Lycium barbarum* extract is well known for its activity against ocular hypertension.

Chiu et al., [28] suggested that *L. barbarum* polysaccharides possess an active role in modulating the immune cells in retina. Ho et al. [54] demonstrated that LB plays an active role in inhibiting glutamate induced cell death and phosphorylation of c-jan N-terminal Kinase (JNK). *Lycium barbarum* plays a prominent role in inhibiting secondary degeneration of retinal ganglion cells and blocking the elevation of p-ERK and p-JNK [52, 54, 78]. Tang et al. [127] suggested that active component of wolfberry-Zeaxanthin and Lutein is specifically involved in the retinal protection in diabetic mice model. Other natural compounds which possess neuroprotective effect are *Centella asiatica* extract [112], Celastrol [4], Trehalose [81, 104], Lycopene [75, 103], Sesamum indicum Linn. [30, 56], Coffee beans extracts [100], *Convolvulus pluricaulis* extract [21] and various flavonoids like naringin, hesperidin, kaempferol, EGCG [30, 82] (Table 1).

### Nanoformulation of natural compounds

The nanotechnology approach of disease treatment has gained a lot of interest over the past few decades. One of the greatest advantages of nanodrug delivery is to increase in the bioavailability and thereby maximizing the therapeutic index of the drug by specifically targeting particular cells or tissues. This helps to reduce the overall side effect of the drug [108]. The small drug molecules are encapsulated within the nanoparticles which transport them to desired location. Although there are various advantages in treating neurodegenerative diseases, the treatment strategy are only temporary satisfaction as the delivery of the drug to the brain is a challenge [118]. Recent advances in the field of nanotechnology are the use of nanoparticles for neurodegenerative diseases [37]. The size range of the nanoparticles helps it to cross various biological barriers within the body especially the blood brain barrier which is a very challenging question [37, 109, 119].

Various studies are carried out to produce nanoformulation of natural compounds, but whether the compound which is nano-encapsulated possesses the same activity as raw remained a question. This has been answered by many studies. Table 2 summarizes the types of nanoformulation of herbal medicine and natural compounds. Curcumin an ancient ayurvedic medicine which is derived from an herb known as turmeric is known for its medicinal properties for many centuries. Some of the disadvantages of curcumin are its low solubility in water and poor bioavailability, so in order to overcome this issue Curcumin nanoparticles are used. One common method in the preparation of Curcumin nanoparticles is by wet-milling technique in which the Curcumin was sprayed into boiling water under sonication and stirring [12]. Studies also suggest that nano Curcumin

had improved solubility, anti-bacterial, and anti-fungal activity when compared to raw Curcumin [12]. Other methods are also used to prepare nano Curcumin particles. Shaikh et al. [38] and Duan et al. [105] prepared nanoparticles using emulsion-diffusion evaporation method which produced stable, spherical nanoparticles. The bioavailability of the molecule becomes drastically high (ninefold increase) when the nanoparticles were administered orally [105]. Another approach is nanoprecipitation a method used to encapsulate Curcumin in polymer (PLGA-PEG) [5, 140].

Similar to curcumin a number of research strategies have been proposed to increase the bioavailability of Resveratrol. Studies suggest that solubility and transport across the plasma membrane of Resveratrol increases when the size is in nanoscale [7]. Some of the disadvantages of Resveratrol are its poor bioavailability, low solubility, and rapid metabolism of the compound [91]. Nano approach helps to overcome these disadvantages. Common method of preparation of Resveratrol nanoparticles is by high shear homogenization technique which produce microparticles and later ultra sound method is used to produce nanoparticles [47, 91]. The tissue concentration in brain, liver and kidney improves when Resveratrol is loaded onto lipid core nanoparticles [43, 106]. Resveratrol incorporated in a biodegradable nanoparticle has been reported for its activity against glioma [106].

Khan et al. [71] suggested that nanoencapsulation of Withaferin-A, an active constituent of *Withania somnifera* tend to increase the anxiolytic activity. Nanoscaled *Ginseng* was produced by using high energy ball milling in which the *Ginseng* extract powder was ground at varying time intervals [136]. The antioxidant capacity and cellular growth ability was tested and it was found to be remarkably high when compared to raw *Ginseng* powder extract [77]. Shinji et al. [110] analyzed the activity of silvanosized *Ginkgo* on brain cells. *G. biloba* nanoparticles were prepared by a combinatorial method of both dry (gas phase grinding) and wet method (liquid phase grinding). Nano-sized *Ginkgo* boost the acetylcholine release from the cortical synapse of the brain cerebral hemispheres [110]. Studies have also suggested that gold and silver nanoparticles are prepared from the leaf extract of natural herbs such as *Baccopa monnieri*, Ashwagandha, *Mucuna pruriens* Linn, *Panax ginseng* root [8, 9, 71, 77, 136].

Polymeric nano-micelles as novel delivery colloid systems which can be applied for nano-encapsulation of poorly water soluble and amphiphilic phenolics. They have a copolymer diblock structure with hydrophilic shell and hydrophobic core. Micelle formation occurs as a result of two forces. Attractive force that leads to the association of molecules and repulsive force prevents unlimited growth of the micelles to a distinct macroscopic phase. Micelle

formation of amphiphilic block copolymers is accompanied with minimizing free energy; change in entropy is generally considered the most important factor to form stable polymeric micelles. The concentration of polymers in solutions is the most important factor during the process of the entropy-driven micelle formation. At very low concentrations, the polymers only exist as single chains. As the concentration increases to a specific value called critical micelle concentration (CMC), polymer chains start to associate to form micelles in such a way that the hydrophobic part of the copolymer is to avoid contact with the aqueous media in which the polymer is diluted [10, 66]. Song et al. [116] successfully loaded anticancerous drug curcumin into the MPEG-P (CL-co-PDO) micelles by a solid dispersion method with a high encapsulation efficiency (>95%). The curcumin-loaded micelles were monodisperse with a PDI less than 0.15 with small particle sizes of approximately 30 nm. Lu et al. [83] fabricated Resveratrol-loaded polymeric micelles based on amphiphilic block copolymer. The effect of Resveratrol-loaded polymeric micelles was studied on the viability and A $\beta$  protection of PC12 cells. The study suggest that Resveratrol-loaded nanoparticles did not show toxicity to cells, and protected PC12 cells from A $\beta$ -induced damage in a dose dependent manner (1–10  $\mu$ M) by attenuating intracellular oxidative stress and caspase-3 activity.

## Electrospinning and electrospaying

### Electrospinning

Electrospinning is a process in which high voltage is applied to a polymer solution which in turn produces electrostatic force at the tip of the needle thereby forming a Taylor cone which elongates into a fluid jet, this charged fluid jet is collected on a grounded collecting device (Fig. 3a). Electrospinning is able to produce nanofibers with diverse forms, such as core-shell fibers, hollow fibers (Fig. 3b) and three dimensional fibers. Electrospun nanofiber has been applied for tissue engineering applications for more than a decade, and it has gained a lot of interest in neural tissue engineering [45, 95, 96].

Corey et al. [33] developed poly(L-lactic acid) (PLLA) nanofiber for serum free growth of primary motor and sensory neurons. The primary motor and sensory neurons (E15) were grown on PLLA nanofiber in a serum free medium. The nanofibers were coated with polylysine for motor neurons and collagen I for sensory neurons. The group suggests that the alignment of neurons grown on substrate was equal to nanofiber alignment and therefore help in investigating the behavior of many neuronal types on electrospun fibers. Kueh et al. [74] investigated on the

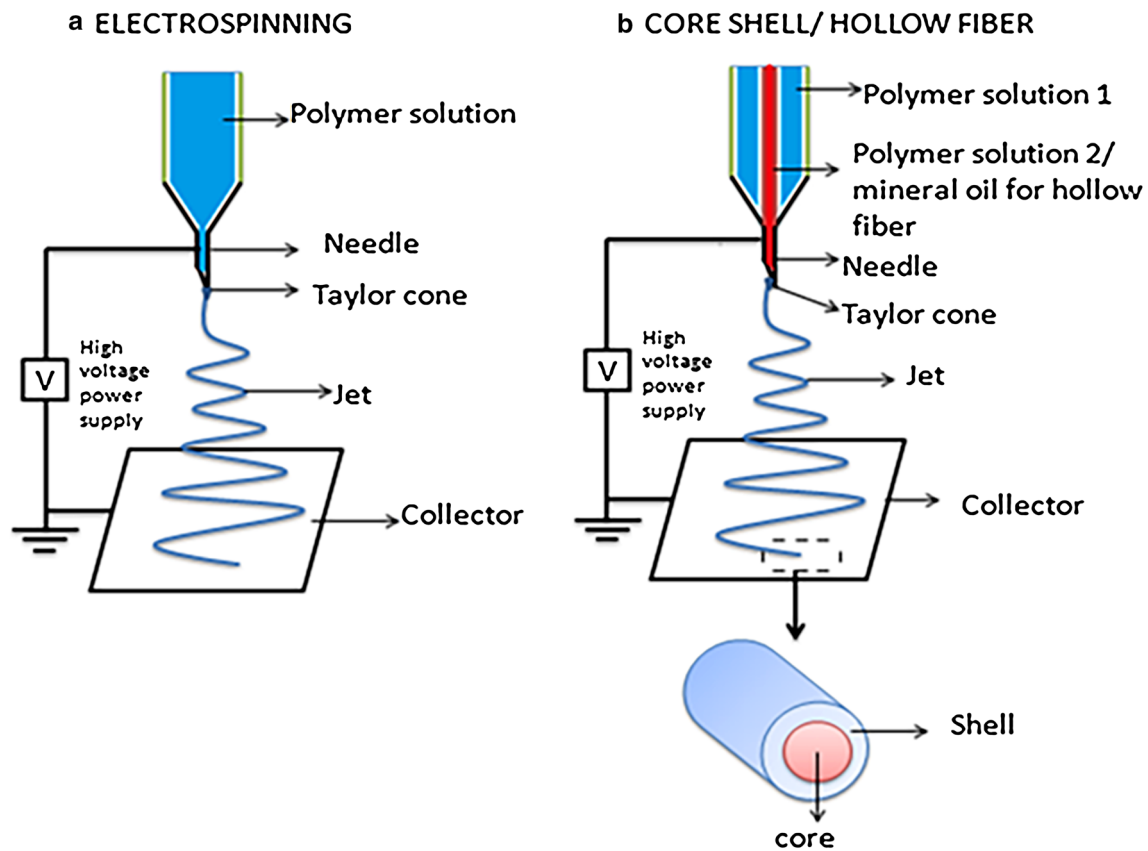


**Table 2** Types nanoformulation of herbal medicine and natural compounds

System	Natural Compounds	Activity	Method	References
Nanoparticles	<i>Bacopa monnieri</i>	Brain tonic- memory boosting	Gold NPs produced by UV cross linking of <i>B. monnieri</i> leaf extract	[9]
	<i>Panax ginseng</i>	Enrich energy, vitality, immune ability and scavenge free radicals	High energy ball milling Gold and silver NPs by green synthesis from the root extract of <i>ginseng</i>	[77, 136]
	<i>Mucuna pruriens</i> Linn	Anti- Parkinsonism	<i>M. pruriens</i> gold NPs	[8]
	Curcumin	Pro-inflammatory activity	Curcumin loaded PLGA particles by emulsion-diffusion—evaporation method Curcumin encapsulated NPs by nanoprecipitation Curcumin encapsulated in alginate- chitosan-pluronic by ionotropic pre- gelation and polycationic cross linking Emulsion polymerization method	[5, 35, 38, 105, 124, 140]
	<i>G. biloba</i>	Brain cell activation	High speed ball milling	[110]
	<i>Ginsenoside</i>	Immune booster	<i>Ginsenoside</i> NPs (ginsomes) prepared using ISCOM matrix technology	[115]
	<i>Withania somnifera</i> (Ashwagandha)	Withaferin A- antioxidant, adaptogenic, anti- inflammatory	Withaferin A- poly (lactic acid) NPs prepared by solvent evaporation method	[71]
Polymeric Nanomicelles	Curcumin	Improve Bioavailability	Solid dispersion method	[116]
	Resveratrol	Good drug loading Protect from $\beta$ -amyloid peptide toxicity Difficult to scale up synthesis techniques	Nano-precipitation method Resveratrol loaded polymeric micelles	[83]
Complex polymers	Curcumin	Release control	Layer By Layer	[147]
	Curcumin	Delivery system for nutraceuticals in liquid foods	Protein–polysaccharide soluble nano-complexes	[55]
Nanocrystal	Curcumin	Enhancing stability	Nanoprecipitation method	[88]
Nanofiber	Curcumin	Pro-inflammatory activity	Electrospinning- Curcumin loaded cellulose acetate fibers Zein fluorescent nanofiber containing Curcumin	[22]
	Resveratrol	Bone regeneration scaffold-sustained release of drug	Electrospun nanofibers	[114]
	<i>Centella asiatica</i>	Crude <i>Centella asiatica</i> (L.) with gelatin for wound healing	Electrospun nanofibers	[113]

construction of olfactory ensheathing cells (OECs) on poly (lactic-co-glycolic acid) nanofiber scaffold which help in the binding of larger lesions in the spinal cord. Nanocomposite electrospinning with quantum dots was used to produce fiber of 250 nm. The OECs from adult rats were cultured on random fiber of 700 and 250 nm fibers. The results showed an increase in cell attachment in nano 700 fiber mesh, and the nano 250 mesh favors bipolarity in cell with unidirectional orientation. The study also suggests that the transplanted OECs helps to bridge damaged areas in the rat spinal cord. Hu et al. [57] modified Poly(glycerol sebacate (PGS) by atom transfer radical polymerization (ATRP) to synthesize PGS- based copolymers with methyl

methacrylate (MMA). This PGS-PMMA was electrospun into nanofiber with fiber diameter of  $167 \pm 33$  nm. Nerve regeneration potential was investigated by seeding rat PC12 cells onto the PGS-PMMA/gelatin nanofiber (Fig. 4a, b). The gelatin containing PGS-based nanofiber acts as a potent candidate in cell proliferation. The cell morphology indicates the ability of the scaffold to induce the neurite outgrowth of the nerve stem cells. Similarly Prabhakaran and Venugopal [97] investigated on the potential of human bone marrow derived mesenchymal stem cells (MSCs) for neuronal differentiation under in vitro condition on poly(L-lactic acid)-co-poly(-3-caprolactone)/collagen (PLCL/coll) nanofibrous scaffolds.



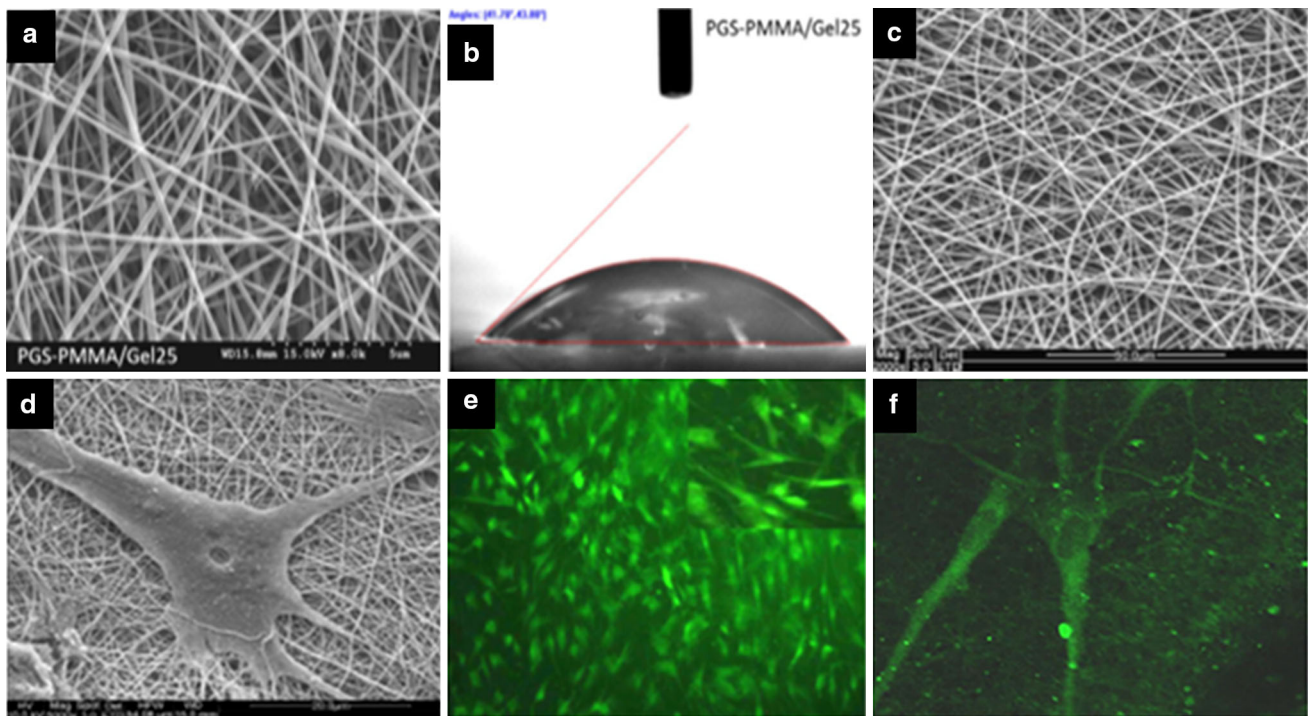
**Fig. 3** a Basic electrospinning set up, b core shell/hollow fiber electrospinning set-up

The study showed that MSCs seeded on the nanofibrous scaffold differentiated and showed neuronal morphology with multipolar elongation and express neurofilament and nestin protein (Fig. 4c–f). Natural/herbal compounds used for electrospinning technique has been widely studied for tissue engineering application, no report has been made for the application of natural/herbal compounds and electrospinning in neurodegenerative diseases. Natural compounds which possess a great potential on neural degenerative diseases, such as wolfberry, *Ginkgo biloba*, *Baccopa monnieri*, *Withania somnifera* and *Ginseng* needs more attention in neural diseases.

Resveratrol loaded poly(caprolactone) serves as an excellent scaffold for bone regeneration due to its sustained release of the drug [114]. Curcumin an constituent of *Curcuma longa* which is known for its anti-tumor, anti-bacterial, anti-inflammatory, anti-oxidant is electrospun using various polymer solution [98, 123]. Suwantong et al. [124] fabricated Curcumin with cellulose acetate and proven non-toxic for dental fibroblast. Curcumin loaded ultrafine zein fluorescent nanofiber are said to possess high fluorescent intensity due to Curcumin incorporation [22]. Electrospun poly (2-hydroxy ethyl methacrylate) loaded with Curcumin is to possess controlled and sustained

release of Curcumin from the nanofibers [98]. Electrospun asiaticoside (from *Centella asiatica* plant) or Curcumin as crude extract or pure substrate to develop tropical/transdermal patch to study the wound healing activity of the herbs [126]. Various factors such as composition, topography, fiber diameter etc. influence the growth of the cells. Christopherson et al. [32] suggested that the fiber diameter plays a vital role in neural stem cell growth. The cell growth and cell spreading is inversely proportional to the fiber diameter.

Wound dressing with herbal extract is a common practice which has been adapted for many decades. The use of electrospun fibers helps in wound healing treatment due to its high porosity and high surface-to-volume ratio which makes it suitable for cell growth by high nutrition infiltration. The active component asiaticoside of a medicinal plant named *Centella asiatica* which is known for its wound healing ability can be electrospun into ultrafine fibers. Sikareepaisan et al. [113] electrospun crude *Centella asiatica* (L.) with gelatin, and *Centella asiatica* plant extract was mixed with gelatin for wound healing. The study suggested that the incorporation of *C. asiatica* into gelatin does not alter the size and morphology of the fibers when compared to that of gelatin fiber mat. Similar



**Fig. 4** **a** SEM images of electrospun PGS-PMMA/Gel25, **b** water contact angles of GS-PMMA/Gel25 (Reprinted from Materials Science and Engineering: C, Hu J, Kai D, Ye H, Tian L, Ding X, Ramakrishna S, Loh X.J, Electrospinning of poly(glycerol sebacate)-based nanofibers for nerve tissue engineering, Copyright (2016), with permission from Elsevier), **c** SEM images of electrospun PLCL, **d** SEM images of MSCs induced to neuronal cells, **e** morphology of

MSCs induced to neuronal cells with multi-polar elongations of neuronal cells, **f** laser scanning confocal microscopic (LSCM) micrographs of MSCs grown using the 'MSC growth media' on PLCL/Coll nanofibers after 28 days of cell culture (Reprinted from Biomaterials, 30/28 [97], Copyright (2009), with permission from Elsevier)

approach was demonstrated with cellulose acetate fiber loaded with *C. asiatica* either as crude or pure substance by Suwanton et al. [125]. Jin et al. [65] studied the skin tissue engineering by electrospinning various plant extract such as *Indigofera aspalathoides*, *Azadirachta indica*, *Memecylon edule* and *Myristica andamanica* by incorporating polymer such as polycaprolactone (PCL). The antibacterial ability of *Tecomella undulata*; a medicinal plant was studied by electrospinning it with PCL/PVP [120]. Opanasopit et al. [93] studied on the release characteristics of mangosteen; a potent antibacterial, anti-inflammatory and anti-oxidant from PVA electrospun fibers.

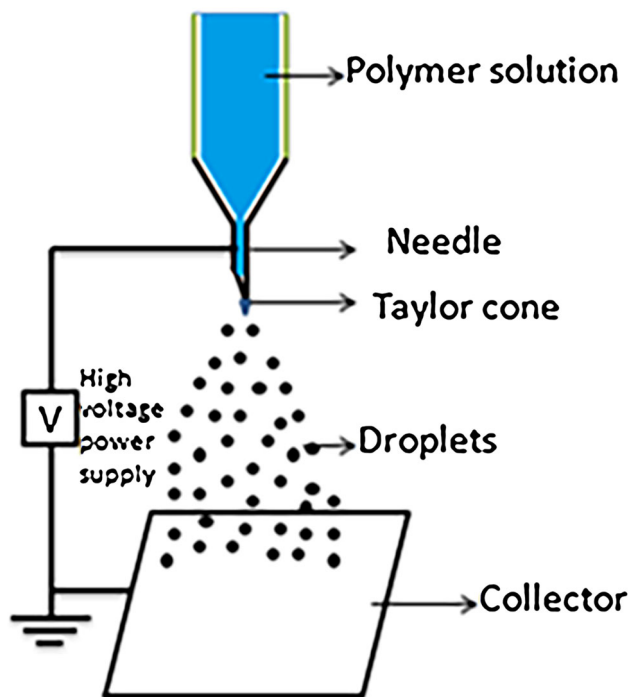
Similar to herbal drugs, compounds such as proteins and flavonoids are also electrospun with various biodegradable and natural polymers to improve its bioactivity. Ji et al. [64] studied on the incorporation of naringin in PCL and PEG-PCL nanoscaffold for treating osteoporosis. Karami et al. [69] studied on the wound healing activity of thymol (a natural monoterpene phenolic derivative of cymene) by electrospinning with polymer such as PCL and PLA. Wang et al. [135] electrospun soy protein isolate with poly(ethylene oxide) and anthocyanin-rich red raspberry extract to study the denaturation and

antibacterial activity and thereby suggested a nanomaterial for food system based on soy protein isolate. Similarly in a study conducted by [121] in which protein and a major component betalactoglobulin was electrospun with PEO (poly ethylene oxide).

### Electrospraying

Another promising technique in the field of nanodrug delivery is electrospraying. Electrospraying is otherwise known as electrohydrodynamic technique following the same principle as that of electrospinning. The experimental setup is made up syringe pump containing polymer solution which is connected to high voltage and a stationary collector (Fig. 5). The jet from the Taylor cone is broken down into droplets producing micro and nanoparticles which are accomplished by altering various properties such as voltage, flow rate etc. [62]. Some of the greatest advantages of electrospraying are size distribution, increase in loading efficiency and the one step process of particle synthesis [117, 145]. The method helps in the direct incorporation of drug into the polymer when compared to other methods of nanoparticle preparation.

## ELECTROSPRAYING



**Fig. 5** Electrospaying technique for fabricating nanoparticles

Electrospaying technique enhances the biocompatibility and efficacy of biomaterials. Kumbar et al. [76] adapted electrospaying technique to coat microsphere scaffold with poly(lactide-co-glycolide) (PLGA) to surface modify the scaffold for implant. The technique is employed to prepare core-shell microspheres. Wu et al. [137] prepared core shell microsphere by electrospaying water-in-oil emulsion of bovine serum albumin (aqueous phase) in a block copolymer (PCL-PPE-EA) dissolved in DCM (oil phase). Electrospaying is also used to prepare nanopowder [46].

Studies also suggest that electrospaying is an excellent technique to encapsulate various drugs for instance; Wang et al. [134] employed electrospaying technique for the preparation of carbamazepine (anticonvulsant drug) nanoparticles which was further annealed at high temperature (above transition temperature) to produce nanocrystals. The study suggests that the solubility of carbamazepine nanocrystals were higher when compared to that of bulk carbamazepine, Wu et al. [138] employed electrospaying technique for the preparation of stimuli-responsive drug particles, Duong et al. [39] investigated on the use of electrospaying technique to encapsulate adjuvant such as imidazoquinoline in an acid-sensitive delivery system for the treatment of Leishmaniasis. This is therefore suggests that electrospaying technique is useful for the

production of pharmaceutical dosage for tissue engineering applications.

## Conclusion and future perspective

The cause of many neurodegenerative diseases still remains a mystery. The use of herbal medicine has gained a lot of interest for their therapeutic potential for many decades. In future, the use of phytochemicals will be a promising approach for neurodegenerative disorders due to their anti-inflammatory, antioxidative and anti-cholinesterase activities. The neurodegenerative disorders such as AD, PD, Huntington's, and others share common features at cellular and subcellular levels as well as sharing mostly common molecular signaling pathways that may lead to apoptosis, necroptosis, and inflammation. Overall use of herbal medicine provides promising alternatives to current therapies for neurodegenerative disorders. However, the potential of herbal medicine/natural compounds is immensely hindered by its poor pharmacokinetic properties. In order to overcome these limitations, the herbal medicine has been incorporated into various drug delivery formulations. Nanoencapsulation has emerged as a promising new area for drug delivery in recent years. Such nanoformulations are able to target drug to specific cells, reducing the required doses and thereby toxicity. Moreover the use of natural compounds in nanosize range as a therapeutic agent has been proven to possess the same activity as in raw. But nanoencapsulation of most of the herbal medicine is still in its infancy. However, electrospinning and electrospaying of herbal medicine and natural compounds for neurodegenerative diseases is still to be explored for fabricating fibers and nanoparticles for neurodegenerative diseases in ageing.

**Acknowledgements** This study was supported by the National Research Foundation Singapore (WBS R-265-000-554-592), Campus for Research Excellence and Technological Enterprise (CREATE) programme, Department of Mechanical Engineering, National University of Singapore, Singapore.

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