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Review Article

Bioactive molecules present in Plants play a potential role in the Treatment of Spasticity in Multiple Sclerosis: a new perspective in Future

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Abstract: Multiple sclerosis (MS) is a chronic disabling disease of the CNS that affects people during early adulthood. Despite several US FDA-approved medications, the treatment options in MS are limited. Many people with MS explore herbal products treatments to help control their MS and treat their symptoms. Surveys suggest that up to 70-80% of people with MS had tried plants products or bioactive compounds of plants for their MS. Patients with MS using herbal products potentially explore a new area for the research. The phyto therapies most frequently used include diet, omega-3 fatty acids and antioxidants. The most promising therapy for the anti-inflammatory and neuroprotective agents in both relapsing and progressive forms of MS were bioactive compounds of plant like flavonoids, vitamin-c, lipoic acid and vitamin D supplementation and others. In future polyphenols, terpenes, alkaloids, anthocyanidine glycosides, plant amines, volatile oils etc. would play a prominent role in the treatment of MS.
Keywords: Multiple sclerosis, Antioxidants, Polyphenols, Lipoic acid, Neuroprotective etc

INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune, inflammatory neurological disease of the central nervous system (CNS) [1, 2]. MS degenerates the myelinated axons in the CNS, damaging the myelin and the axons to varying degrees [3, 4]. Alone in the U.S., around 250,000 to 350,000 people were diagnosed with MS [5]. Genetically, women are 2-fold more prone for MS than men. Demographical data suggests that people of North European descent are at high risk for MS [2, 7]. MS typically presents in adults 20 to 45 years of age. Sparsely it presents in childhood or middle age [7]. Though the etiology appears to be intricate, this immunological, autoimmune disorder appears to be an amalgamation of genetic susceptibility and non-genetic trigger. Ancillary tests such as MRI and CSF (Cerebro Spinal Fluid) examination offers a lucid diagnosis bolstering the clinical evidences [7].

The patients may be grouped into four major categories:

1. Relapsing–remitting MS: the most common form, affecting about 85% of MS patients. It is marked by flare-ups (relapses or exacerbations) of symptoms followed by periods of remission, when symptoms improve or disappear.
2. Secondary progressive MS: may develop in some patients with relapsing–remitting disease. For many patients, treatment with disease-modifying agents helps delay such progression. The disease course continues to worsen with or without periods of remission or levelling off of symptom severity (plateaus).
3. Primary progressive MS: affects approximately 10% of MS patients. Symptoms continue to worsen gradually from the beginning. There are no relapses or remissions, but there may be occasional plateaus. This form of MS is more resistant to the drugs typically used to treat the disease.
4. Progressive-relapsing MS: a rare form, affecting fewer than 5% of patients. It is progressive from the start, with intermittent flare-ups of worsening symptoms along the way. There are no periods of remission. More than 30% of MS patients have moderate-to severe spasticity, mostly in the legs. Initial clinical findings in MS patients are often sensory disturbances, the most common of which are paresthesias (numbness and tingling), dysesthesias (burning and “pins and needles”), diplopia, ataxia, vertigo, and bladder (urinary

sphincter) disturbances, optic neuritis, fatigue occurs in 90% of patients, sexual dysfunction.

DISEASE MODIFYING THERAPIES

The primary objective of the existing disease modifying therapies is to subside the recurrent exacerbations. No curative, FDA-approved therapies for MS are currently available. Symptomatic treatments are aimed at maintaining function and improving quality of life [9].

FDA-Approved Disease-Modifying Agents for the Treatment of Multiple Sclerosis				
Drug	**Brand (Manufacturer)**	**Recommended Dose**	**Dosing Frequency**	**Route**
Interferon beta-1a	Avonex (Biogen Idec)	30 mcg	Once weekly	IM
Interferon beta-1a	Rebif (Pfizer)	22 or 44 mcg	Three times weekly	SQ
Interferon beta-1b	Betaseron (Bayer)	0.25 mg	Every other day	SQ
Interferon beta-1b	Extavia (Novartis)	0.25 mg	Every other day	SQ
Glatiramer acetate	Copaxone (Teva)	20 mg	Once daily	SQ
Mitoxantrone	Novantrone (EMD Serono)	5 to 12 mg/m2	Short infusion (about 5 to 15 minutes) every 3 months	IV
Natalizumab	Tysabri (Biogen Idec)	300 mg	1-hour infusion every 4 weeks	IV
Fingolimod	Gilenya (Novartis)	0.5 mg	Once daily	PO
IM = intramuscular; IV = intravenous; PO = per os (by mouth); SQ = subcutaneous.				

OFF-LABEL TREATMENT OPTIONS

The following therapeutic agents have not been approved by the FDA for the treatment of MS, but physicians often use them off label for this purpose: azathioprine (Imuran), methotrexate, cyclophosphamide, mycophenolate mofetil (Cell Cept) and cladribine etc.

DRUGS IN DEVELOPMENT

Several agents aimed at treating MS are currently in the research pipeline are: laquinimod, teriflunomide (Aubagio), BG-12 (Dimethyl Fumarate), daclizumab (Zenapax), alemtuzumab, (Campath/Lemtrada), rituximab (Rituxan), ocrelizumab and ibudilast etc.

List of the Medicinal Plants Used for the Treatment of Multiple Sclerosis:

S.No	**Vernacular Name & Family**	**Parts used**	**Extract**
1.	Agrimoniaeupotoria (Rosaceae)	Flower	Aqueous
2.	Echinaceae purpurea (Astraceae)	Flower	Ethanolic
3.	Gingko biloba (Ginkgoaceae)	Leaves and seeds	Methanolic
4.	Hypericumperforatum (Hypericaceae)	Flowers	Alcohol/water
5.	Metricariareticutita (Compositae)	Flower	Alcoholic
6.	Valerian officinalis (Caprifoliaceae)	Flower	Alcoholic
7.	Panax ginseng (Araliaceae)	Root	Aqueous
8.	Vacciniummacrocarpon (Ericaceae)	Berries	Alcoholic
9.	Oenotherabiennis (Ongaraceae)	Flower oil	Ethanolic
10.	Cannabis sativa (Cannabinaceae)	Whole plant	Alcoholic
11.	Menthapiperita (Lamiaceae)	Leaves	Alcoholic
12.	Berberis vulgaris (Berberiaceae)	Berries	Aqueous
13.	Arctiumatlanticum (Asteraceae)	Root	Aqueous
14.	Salvia officinalis (Lamiaceae)	Leaves, Flower	Alcoholic
15.	Centella asiatica (Apiaceae)	Leaves	Alcoholic
16.	Vacciniummyrtillus (Euricaceae)	Leaves, Fruit	Methanolic
17.	Nepetacataria (Lamiaceae)	Flower	Aqueous
18.	Stachys officinalis (Lamiaceae)	Flower	Alcoholic

HERBAL AND NATURAL PRODUCTS AND THE DISEASE PROCESS

Current Medications in Clinical Use:

A standard method of treating MS itself is the use of beta interferons, particularly 1b (Betaseron) and 1a (Avonex) [10]. In general, in response to a foreign stimulus, the body makes proteins known as interferons. There are several types of interferons. Beta interferon is used for MS because it seems to calm the immune system (another type of interferon, gamma, tends to

stimulate the immune system). As noted in the Etiology chapter, the autoimmune theory of MS suggests that the immune system appears to be overactive. Therefore, using beta interferons that calm the immune system, rather than gamma interferon that stimulates it, makes sense given the assumptions of the autoimmune theory. However, it is equally important to note, however, that, in spite of the approved use of beta interferons, they do not cure MS. Rather; they seem to decrease the relapse rate, increase the time between attacks and decrease the severity of attacks. In addition, their use seems to decrease the amount of damage detected on follow-up MRI scans [10]. Unfortunately, while both types of beta interferons have beneficial uses, they also have severe side effects. The possible side effects include fever, nausea, and skin reaction at the sight of injection. If interferons are used in an attempt to manage the disease process and if side effects occur as a result, specific herbal remedies may be used in an attempt to alleviate them.

a. *Agrimoniaeupotoria* (Rosaceae)
Description: Agrimonia commonly known as Agrimony is a genus of 12 to 15 species of perennial herbaceous flowering plants native to the temperature regions of the northern hemisphere with one species also in Africa. The species grow to between 5to 12 m tall with interrupted pinnate leaves and tiny yellow flowers born on a single spike.
Major constituents: 10% tannins, bitter glycosides, coumarins, flavonoids and vitamins B & K
Mechanism of action: Mesaconitine inhibited motor coordination and motor activity and demonstrated weak sedative effects in animal models. Ignavine displayed no sedative effects.
Pharmacodynamic uses: Anti-diarrhoeal, anti-inflammatory, anti-spasmodic, anti-viral, bitter tonic, disorders of the gall bladder, liver and kidney.

b. *Echinacea purpurea* (Astraceae)
Description: It is known as purple cone flower. It is a North American species of flowering plant. It is a native to Eastern North America. It is an herbaceous perennial upto 120 cm tall 25 cm wide. Its cone shaped flowering heads purple in the wild. Its individual flowers, within the flower head are hermaphroditic.
Major constituents: Flavonoids, glycosides, inulin, volatile oil, vitamins and minerals.
Mechanism of Action: Stimulates the immune system
Pharmacodynamic Uses: Anti-inflammatory, Cold, Upper respiratory tract infection.

c. *Gingobiloba* (Ginkgoaceae)
Description: Ginkgos are large trees, height of 20 to 35 m. the trees are angular crown and long. The leaves turn a bright yellow, then fall, that will grow in environments that are well-watered and well-drained.
Major constituents: Phenolic acids, flavonoids, glycosides, terpenes, polyprenols.
Mechanism of Action: Inhibit the Platelet Activating Factor (PAF)
Pharmacodynamic uses: Improve memory and mental clarity, reducing dizziness, vertigo, antispasmodic, vision problems.

d. *Hypericumperforatum* (Hypericaceae)
Description: It is native to parts of Europe and Asia but has spread worldwide as a cosmopolitan invasive weed. It is a herbaceous perennial plant with extensive, creeping rhizomes. The leaves are yellow green in colour. The pollen grains are ellipsoidal.
Major constituents: Flavonoids, rutin, isoquercetin, quercetin, tannins, vitamins, phenolic acids, alkanols.
Mechanism of Action: Stimulate the immune system
Pharmacodynamic uses: Anti-inflammatory, mental health problems, wounds, burns, treatment of depression.

e. *Matricariarecutita* (Compositae)
Description: It is a low growing plant, creeping or tailing. Its tufts of leaves and flowers a foot high. The root is perennial, jointed fibrous, the stems hairy and freely branching. The fruit is small and dry. The whole plant is greenish in colour.
Major constituents: Glycosides, flavonoids, volatile oils.
Mechanism of Action: Inhibition of GABA receptors are stimulated in CNS
Pharmacodynamic uses: Anti-anxiety, anti-spasmodic, tonic, heamorrhoids, insomnia, gastrointestinal problems.

f. *Valerian officinalis* (Caprifoliaceae)
Description: It is a perennial flowering plant, with heads of sweety centered pink or white flowers tha bloom in the summer. Valerian flower extract were used as a perfume in the16th century. Native to Europe and parts of Asia.
Major chemical constituents: Alkaloids, flavonoids, volatile oils, iridoids.
Mechanism of Action: Inhibition of GABA receptors is stimulated in CNS by valerian.
Pharmacodynamic uses: Hypnotic, sedative, anti-anxiety, anti-inflammatory, anti-spasmodic.

g. *Panax ginseng* (Araliaceae)
Description: Ginseng is found in North America and in Asia, typically in cooler climates. It is a perennial herb with large, fleshy, slow growing root 2 to 3 inches in length and ½ to 1 inch thickness. It is pale yellow to brownish colour.
Major chemical constituents: Saponins, phytosterols, carbohydrates, sugars, organic acids, vitamins, minerals, ginseng oils.
Mechanism of Action: It has been used to both stimulate and relax the nervous system. It increases capillary circulation in the brain and decreases the effect of stress.

Pharmacodynamic uses: Aphrodisiac, stimulant used in depression, fatigue, hair tonic, cosmetics.

h. *Vacciniummacrocarpon* (Ericaceae)
Description: These are low creeping shrubs upto 2 m long and 5 to 10 cm in height. They have slender wiry stems that are not thickly woody and have small evergreen leaves. The flowers are dark pink with very distinct reflexed petals. The fruit is a berry that is larger than the leaves of the plant.
Major chemical constituents: Polyphenols, tannins, flavonoids, quercetin, proanthocyanidins.
Mechanism of Action: Medical management has included hormone replacement therapy and alpha-adrenergic agonists, but questionable results and intolerable risks have shifted this mode to serotonin-norepinephrine reuptake inhibitors, which have CNS action.
Pharmacodynamic uses: Urinary tract infections, antioxidant, fungal infections.

i.*Oenotherabiennis* (Ongaraceace)
Description: It is the oil from the seeds of the evening primrose plant. It is herbaceous flowering plant native to the Americans.
Major chemical constituents: Omega-6-fatty acids, gama-linoleic acid (GLA).
Mechanism of Action: Gama-linoleic acid suppresses immune function, therefore useful in multiple sclerosis.
Pharmacodynamic uses: Eczema, psoriasis, alzeimers disease, osteoporosis, rheumatoid arthritis.

J.*Canabis sativa* (Cannabinaceae)
Description: These are dried leaves, flowers, stems, seeds from the hemp plant. It is an annual herb, stems variable upto 5 m tall, with resinous pubescent, angular, hallow pairs of true leaves.
Major chemical constituents: Cannabidiol, cannabinol, tetra hydro cannabinol.
Mechanism of Action: When person smokes marijuana, THC quickly passes from the lungs into blood stream. The blood carries the chemical to the brain and the other organs throughout the body. THC acts on specific brain cell receptors that ordinarily react to natural THC in the brain.
Pharmacodynamic uses: Hypnotic, sedative, analgesic, anti-inflammatory, hallucinogenic.

k. *Withania somnifera* (Solanaceae)
Description: This species is a short, tender perennial shrub growing 35 to75 cm tall. Tomentose branches extend radially from a central stem. Leaves are dull green, elliptic, usually upto 10 to 12 cm long. The flowers are small, green and bell shaped. The ripe fruit is orange red.
Major chemical constituents: Alkaloids, steroidal lactones.
Mechanism of Action: Activity in GABA and slightly enhanced Acetyl choline Esterase activity.
Pharmacodynamic uses: Antiinflammatory, Antitumor, Antistress, antioxidant, Immunomodulatory, Hemopoietic.

l. *Menthapiperita* (Lamiaceae)
Description: It is herbaceous rhizomatous perennial plant growing to30 to 90 cm tall with smooth stem square in cross section. The leaves are from 4 to 9 cm long and 1.5 to 4 cm broad, dark green with reddish veins, with an acute apex and coarsely toothed margins.
Major chemical constituents: Volatile oils like menthol, menthone, carboxyl esters, limonene, pinene, caryophyllene.
Mechanism of Action: Oil reduced contractions evoked by potassium depolarization and calcium contractions evoked in depolarizing Krebs solution.
Pharmacodynamic Uses: Irritable bowel syndrome, carminative, anti-spasmodic, anti-bacterial, nerve pains.

m. *Berberis vulgaris* (Berberidaceae)
Description: It has dimorphic shoots, long shoots which form the structure of the plant and short shoot only 1 to 2 mm long. The leaves on long shoots are non-photosynthetic. The leaves are 1 to 10 cm long, simple and either entire or with spiny margins.
Major chemical constituents: Isoquinoline alkaloids especially berberine.
Mechanism of Action: Stimulate the immune system.
Pharmacodynamic Uses: Anti-inflammatory, antimicrobial, anti-diarrhoeal, polycystic ovary syndrome.

n. *Arctiumatlanticum* (Asteraceae)
Description: Plants of the genus Arctium have dark green leaves. They can grow upto 28 cm long. They are large, course, ovate with the lower ones being heart shaped. They are woolly underneath. The leaf stalks are generally hollow.
Major chemical constituents: Phytosterols, fatty acids, lactones, flavonoid glycosides, arctin.
Mechanism of Action: It increases the immunological activity and anti-inflammatory activity by inhibiting Platelet Activating Factor (PAF).
Pharmacodynamic Uses: Diuretic, diaphoretic, blood purifying agents, contact dermatitis.

o. *Salvia officinalis* (Lamiaceae)
Description: It is a perennial, evergreen sub-shrub with woody stems, greyish leaves and blue to purplish flowers. They grow 2 f.t tall and wide, with lavender flowers. The plant flowers in late spring.
Major chemical constituents: Essential oils, tannic acid, oleic acid, flavones, flavonoid glycosides.
Mechanism of Action: Essential oils inhibit the AChE activity.
Pharmacodynamic uses: Gastritis, diarrhoea, heart burn, Alzheimer's disease, depression and memory loss.

p. *Centella asiatica* (Apiaceace)

Description: It is a small, herbaceous, frost-tender perennial plant. The stems are slender, creeping, stolous, and green to reddish green in colour. It has long, stalked, green, rounded apices which have smooth texture with palmately netted veins. Flowers are white or pinkish to red in colour.

Major chemical constituents: Triterpenoids, phytosterols, volatile oils, tannins, vitamins B & C

Mechanism of Action: Reduce anxiety and increase mental functions. Restores the axon and transmits the nerve impulses.

Pharmacodynamic uses: Mental clarity, wound healing, anti-stress and treatment of skin conditions like leprosy, psoriasis.

q. *Vacciniummyrtillus* (Ericaceae)

Description: It is also known as Black Hearts. Bilberry bush is a close relative of American Blue Berries. It flourishes in damp acidic soil throughout temporal and subartic regions of the world.

Major chemical constituents: Quercetin, isoquercetin, gallic acid, benzoic acid, caffic acid, epicatechin, flavanols, tannins.

Mechanism of Action: It enhances the dopamine release and improves neuronal communication and it increases the triiodothyronine transport to different regions of brain.

Pharmacodynamic uses: Antimicrobial, anti-inflammatory, antioxidant, CVS disorders, dementia.

r. *Nepetacataria* (Lamiaceae)

Description: It is a short lived herbaceous perennial growing 50 to 100 cm tall and wide. It resembles a typical mint family member in appearance by having the characteristic square stem with brown-green foliage. The course-toothed leaves are triangular to ovate. The flowers can be white and spotted with pale purple or pink.

Major chemical constituents: Essential oils, triterpenoid nepetalactone, tannins, iridoids.

Mechanism of Action: Cantip oil and nepetalic acid induce sleep and decrease performance.

Pharmacodynamic uses: Antifungal, antimicrobial, CNS stimulant.

s. *Stachys officinalis* (Lamiaceae)

Description: It is a perennial grassland herb growing to 30 to 60 cm tall. Its leaves are stalked on upright stems, narrowly oval, with a heart shaped base, with a wrinkled texture and toothed margins.

Major chemical constituents: Glycosides, flavonoids, tannins.

Mechanism of Action: It calms, nourishes the nervous system. It reduces the impact that stress has on the body and fights nervous exhaustions.

Pharmacodynamic uses: Antianxiety, gall stones, heart burn, blood pressure, migraine, neuralgia and prevent sweating.

RESULTS AND DISCUSSION

Treatments for MS are divided into two large categories: those that are intended to control the disease process and those that help to manage symptoms. Pharmacological agents that intend to control the disease process besides human recombinant IFN-β and glatiramer acetate include a monoclonal antibody against α-4 integrin, natalizumab and a chemotherapy agent, mitoxantrone. These therapies reduce the frequency of relapses and new lesion formation in the brain and reduce the risk of increased disability among patients with relapsing MS. However, these therapies are ineffective in progressive forms of MS, only partially effective in relapsing MS, only available in injectable forms, have significant side effects and are very costly. Common symptoms that MS patients suffer from include fatigue, depression, cognitive impairment, spasticity, pain and imbalance. These symptoms can have a significant negative impact on the patient's quality of life; hence, treatment targeting these is critical. Pharmacologic or rehabilitative treatments can help with these symptoms to a variable extent but care is still not optimal; therefore, the development of more effective and affordable symptomatic therapies remains a critical goal of MS care.

There is a paucity of well-designed clinical trials assessing the benefit of alternative therapies for treating MS. High-use therapies, which include diet, omega 3 FAs and antioxidants, may have potential benefit in MS as they have immunomodulatory and neuroprotective properties when evaluated in animal models, MS patients and in other chronic disease conditions. Diet, omega-3 FAs and antioxidants also appear to have a high safety profile when used at recommended doses. Omega-3 FAs are a family of polyunsaturated FAs (PUFAs) that contain a common carbon–carbon double bond at the third carbon from the terminal methyl end of the molecule. The parent omega-3 FA is linolenic acid. It is an 'essential fatty acid' and cannot be synthesized in humans and therefore must be supplied in the diet. Sources high in linolenic acid are plant-based and include flaxseeds and flaxseed oil, soy and soybean oil, and canola oil. Eicosapentanoic acid (EPA) and docosahexanoic acid (DHA) are two omega-3 FAs that are synthesized from linolenic acid through a series of enzymatic steps [45]. While EPA and DHA can be synthesized from linolenic acid in humans, a rate-limiting enzymatic conversation from linolenic acid to EPA and DHA results in a very low conversion rate to EPA and DHA [46].

Unlike plant oils, which contain no EPA and DHA, fish and fish oils contain high levels of EPA and DHA, particularly cold water fish (e.g., salmon and mackerel). DHA can cross the blood–brain barrier and, along with arachidonic acid, is a major component of neuronal cell membranes [47, 48]. EPA can be converted

to prostaglandin I_3 and E_3, thromboxane A_3 and leukotriene B_5, and therefore has immunomodulatory capacity, acting as an anti-inflammatory agent [45, 49].

There is mounting scientific data supporting the role of immune-mediated mechanisms in the pathogenesis of MS. T cells, B cells, and macrophages, along with soluble mediators of inflammation, appear to cause demyelination and axonal and neuronal injury in MS. One common pathway of tissue injury in MS is oxidative stress mediated by reactive oxygen species [50]. The notion that oxidative stress–mediated lipid peroxidation of brain tissue contributes to the pathogenesis in MS is emphasized in recent studies. Serum lipid peroxi- dation generation can be estimated by thiobarbituric acid (TBA) reactivity and has been used to assess the oxidative stress levels. Because of the interest in free radical injury in MS, it is not surprising that various antioxidants such as lipoic acid, vitamin C, vitamin E, and flavonoids, among others, are being explored as having a potential role in prevention or treatment of MS which are present in different parts of plants. For an example Gingko attracted the interest of MS researchers because of its potential as a disease modulatory agent as well as a treatment for cognitive dysfunction in MS. How- ever, gingkolide B, which is a specific compound found in gingko biloba extracts that had beneficial effects on EAE, did not have effects on exacerbations in a double-blind, placebo-controlled trial of MS [51, 52]. Gingko biloba has been studied as a treatment for cognitive dysfunction in MS in two clinical trials.

CONCLUSION

The clinical applications of β-INT still remain in question due to their adverse effects. In the current clinical space of MS, herbals and nutraceuticals could be thoroughly investigated to fill in the lacunae in the treatment of MS.

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