# Advanced Herbal Medicine

# Research paper

***"Can components of Vitex agnus-castus* (Chaste Tree) *cross the blood-brain barrier and exert disease-modifying $D_2$ receptor activity in a human model of Parkinson's disease?"***

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**Introduction**

Parkinson's Disease (PD) is a chronic neurodegenerative movement disorder characterized by substantia nigra cell death and subsequent loss of dopamine (Natural Standard 2009, p.1). Prevalence is 160/100,000 in Western Europe, afflicting 4% of the population over 80 (Davie 2008, p.109). In the United States, 50,000 new diagnoses are made annually (Natural Standard 2009, p.1).

Contemporary orthodox medications may improve symptoms initially, however no drugs can alter the course of PD; in fact, those drugs currently in use need to be avoided until they are clinically necessary, owing to delayed side effects (Kumar & Clark 2005, p.1229). This allows for disease progression and worsening of symptoms.

Around half of PD sufferer's experience minor or major side effects after five years of treatment. For example, a recent retrospective study has shown that PD medication use is associated with an increased frequency of compulsive gambling and hypersexuality (Bostwick et al 2009, p.310). Moreover, the primary treatment drug Levodopa (L-dopa), which gradually becomes ineffective after several years even with increasing doses, leads to development of Levodopa-induced dyskinesia, itself a movement disorder (Kumar & Clark 2005, p.1230).

With an average age of onset of 60 years (Tortora & Grabowski 2003, p.521) and an aging population, it is increasingly inherent that novel and efficacious treatment strategies are evolved to combat this debilitating condition.

**Herbal Medicine Management of Prkinson's Disease**

*Claviceps purpurea:* This fungus which inhabits damp rye grains, comprises the ergot alkaloids from which the PD drugs bromocriptine (a central dopamine (DA) agonist), pergolide and cabergoline are derived (Bryant, Knights & Salerno 2005, p.330). While not as effective as L-dopa, the ergot derivatives have shown to improve bradykinesia and rigidity via central DA receptor stimulation and many patients unresponsive to L-dopa therapy have improved with the addition of pergolide (Bryant, Knights & Salerno 2005, p.332).

In contrast, the results of a fourteen year study comparing three initial treatments in PD found that early treatment with bromocriptine failed to reduce mortality or motor disability and, while motor complications were initially reduced, the effect was not sustained (Katzenschlager et al 2008, p.474).

Cabergoline has been shown to have a high affinity for stimulation of the post-synaptic $D_2$ and $D_3$ (dopamine) receptors. However, evidence of fibrotic degeneration of cardiac valves has been reported with the use of this, and the other ergot-derived agonists and regular monitoring including echocardiography is necessary (Davie 2008, p.109).

*Mucuna pruriens:* Commonly known as 'Cowhage', the seeds of this leguminous plant contain L-dopa and have been used traditionally in Ayurvedic medicine for the treatment of PD (Hussain & Manyam 1997, p.419). The L-dopa pathway involves conversion of dietary phenylalanine and tyrosine in adrenergic nerves to dopa (dihydroxyphenylalanine), which is the immediate precursor for DA (Bryant, Knights & Salerno 2005, p.328).

A study of the clinical effects and pharmacokinetics of *M. pruriens* preparation revealed that the plant induced a considerably faster onset of action, shorter latencies to peak L-dopa plasma concentrations, 110% higher plasma concentrations and no observable differences in dyskinesias or tolerability compared with standard L-dopa/carbidopa preparations in PD patients (Katzenschlager et al 2004, p.1672).

Hussain and Manyam (1997, p.419) advance that *M. pruriens* seed may have unidentified antiparkinsonian compounds additional to L-dopa, or it may contain adjuvants which enhance the efficacy of L-dopa. However, research findings by Kasture et al (2009, p.111), while strongly supporting its antiparkinsonian activity, found the extract incapable of exerting neuroprotective effects due to its failure in preventing either

tyrosine hydroxylase decrease or astroglial/microglial activation in a rodent model. The usefulness of this plant may rest with its potential as an adjuvant, rather than a monotherapy; further research is needed to determine its precise role in PD.

*Gingko biloba:* Little is known about the pharmacokinetics of *G. biloba* although there is increasing interest in its potential application in neurodegenerative disease such as PD, resulting from its known mitochondrial and neuroprotective effects (Braun & Cohen 2007, p.352). PD is frequently associated with oxidative stress and defective cellular protective mechanisms and a study has confirmed that extract of *G. biloba* (EGb 761) has the capacity to increase the antioxidant enzymes catalyase and superoxide dismutase, while lowering lipid peroxidation in rat brain (Bridi et al 2001, p.449).

Another study found that, while oral EGb 761 significantly increased the cerebral cortex uptake of serotonin in mice, it failed to do so with dopamine (Ramassamy et al, cited in Braun & Cohen 2007, p.347). Therefore, *G. biloba* appears confined to a protective role in PD, perhaps as an early treatment to slow disease progression, or as a preventative measure in conjunction with other therapies.

*Hypericum perforatum:* Widely employed in depressive and nervous conditions, *H. perforatum* seems an unlikely candidate for the treatment of PD at first glance. However, evidence shows that this herb can exert neural protection and treatment of oxidative stress. A century ago, the Eclectics favoured *H. perforatum* as having an undoubtedly strong influence upon the nervous system, and placed spinal injuries, spinal concussion and prevention of tetanic complications amongst its potential indications (Felter 1922).

In the present day, evidence has emerged which suggest standard extracts of *H. perforatum* (SEHP) may have an application in neurodegenerative diseases such as PD. The results of a Chinese study assessing the effect of SEHP on $H_2O_2$-damaged PC12 (neural) cells, revealed that the extract capably exerted antioxidative and neuroprotective activity, as it (i) Facilitated growth rate of the cells at concentrations of 1~100μm/ml and markedly increased cell viability compared to the control group; (ii) Showed a greatly increased protective activity in a dose-dependent manner, peaking at 40μm/ml with an improvement of 133% compared with controls; (iii) Easily entered cells and greatly decreased ROS levels with increasing concentrations of SEHP, to a significantly lower level than controls; and (iv) Effectively blocked DNA fragmentation of $H_2O_2$-induced

apoptosis in PC12 cells, preventing cell shrinkage and apoptosis at concentrations of 10~100μm/ml (Lu et al, 2004, p.397).

Rather than act as a competitive inhibitor at transmitter binding sites, constituents of *H. perforatum*, specifically hyperforin, are known to affect the sodium gradient which results in greater inhibition of neurotransmitter uptake. This increases availability of DA, as well as serotonin, noradrenaline, GABA and L-glutamate (Muller 2003, p.101). Evidently antioxidant, neuroprotective and dopaminergic activity are potential indications for its use, while prolactin inhibition has also been shown. In support, administration of *H. perforatum* significantly reduced plasma prolactin in human and animal models, possibly via a DA-mediated mechanism, causing a concomitant rise in brain cortical tissue DA (Franklin & Cowen 2001, p.29).

Furthermore, depression is known to be the commonest mood disturbance in PD, occurring in up to 50% of cases (Dooneief, cited in Davie 2008, p.109). Given what is already known about the antidepressant effect of *H. perforatum*, this phytotherapeutic agent may well have a clinical basis in both treating the depressive symptoms of PD and perhaps altering or deferring disease progression altogether. Further clinical research certainly appears warranted.

*Vitex agnus-castus:* Otherwise known as Chaste Tree, *V. agnus-castus* was used historically to suppress libido and was prescribed for the treatment of giddiness and salivation (Felter & Lloyd 1898, p.2056). Castleman (2001, p.143) asserts that, apart from rare and minor cases of stomach upset and urticaria, the herb is not associated with any significant side effects.

Research conducted nearly a decade ago revealed *V. agnus-castus* to contain at least two different compounds with the ability to impart dopaminergic activity. The first are hydrophilic, thermolabile dopamine agonists and the second, lipophilic, thermostable endocrine active compounds (Bone 2001, p.30). The lipophilic compounds have been identified as bicyclic diterpenes, namely rotun-difuran and 6beta,7beta-diacetoxy-13-hydroxy-labda-8,14-diene and have shown an affinity for $D_2$ receptors *in vitro* (Meier et al 2000, p.373).

Activation of the $D_2$ receptor by dopamine-like compounds such as the diterpenes, causes a reduction in cAMP synthesis, inhibition of prolactin secretion (Bone 2001, p.30) and enhanced availability of dopamine (Bone & Morgan 2001, p.1). The prolactin-suppressive properties of *V. agnus castus*' dopaminergic compounds have proven comparable in their effects to dopamine itself (Wuttke et al 2003, p.348).

An *in vitro* study revealed that *V. agnus-castus* could displace sulpiride (a DA receptor antagonist) from dopamine $D_2$ receptors, providing further evidence of a receptor affinity for the extract (Bone & Morgan 2001, p1). According to Bone and Burgoyne (2005, p.1) new diterpene constituents of *V. agnus-castus* are still being discovered and to date, the most active of these are relatively non-polar and probably cross the blood-brain barrier (BBB). The authors propose that this being the case, *V. agnus-castus* may be a beneficial adjunct in the treatment of PD.

**Research Proposal**

Evidence of weaknesses and gaps in the contemporary model of PD treatment and an observed lack of novel therapeutic agents indicate a need for further research. Scientific data determining the efficacy of phytotherapeutic agents in the treatment of PD is insufficient, although the available research is promising.

To summarise the weaknesses, (i) first-line treatments require delayed administration owing to side effects, allowing for disease progression and symptom deterioration; (ii) The afflicted face distressing and progressive disability and suffering; (iii) Compulsive gambling, hypersexuality, Levodopa-induced dyskinesia and fibrotic degeneration of cardiac valves comprise some of the known side effects of drug treatment; (iv) Symptom alleviation is often unsustained; in fact, Rascol (2009, p.51) infers that presently, no "disease modification" study design exists, nor has a drug been approved for that indication.

Research has also revealed gaps in current knowledge. For example, disagreement abounds regarding which treatment approach is potentially more efficacious. Some agree that treatment should aim to replace dopaminergic transmission at striatal synapses (Sujith 2009, p.105) while others maintain that neuroprotective compounds which prevent dopamine cell death are the answer (Rascol 2009, p.51).

Until this question is answered, it is unknown (from a naturopathic point of view) whether a dopaminergic agonist or an antioxidant, neuroprotective agent is better indicated. It also remains to be seen whether the herbs discussed (*H. perforatum, G. biloba, M. pruriens* and *V. agnus-castus*) can exert disease-modifying effects in human models of PD and indeed, whether *V. agnus-castus* can in fact cross the BBB.

In addressing the latter, it is proposed that a controlled, randomized trial in human volunteer's with early-onset PD be conducted, involving administration of *V. agnus-castus* versus placebo to determine whether *Vitex* can in fact cross the BBB and exert disease-modifying, $D_2$ receptor activity.

It is recommended that *V. agnus-castus*, 2,000mg/day in divided doses (4 x 500mg tablets daily) be given, standardized to contain sufficient levels of diterpenes in order to exert significant dopaminergic effect (Bone & Burgoyne 2005, p.2). Placebo will be used as a control to eliminate the possibility of extraneous variables and achieve internal validity (Polgar & Thomas 2000, p.48).

Given that most participants are expected to have an average age of 60 years (Tortora & Grabowski 2003, p.521), oral administration of tablets is considered an appropriate route, due to it being minimally invasive or distressing. The study has a proposed length of 3 years to allow observation of clinically relevant changes (Rascol 2009, p.51).

**Research Question**

**"Can components of *Vitex agnus-castus* (Chaste Tree) cross the blood-brain barrier and exert disease-modifying $D_2$ receptor activity in a human model of Parkinson's Disease?"**

*1.Research design methods:* Double-blind, placebo-controlled, randomized human trial of three years duration is proposed, with a pre-test design allowing for measurement of actual changes in individual cases (Polgar & Thomas 2000, p.61). Baseline evaluations will utilize existing PD assessment tools (see *data collection methods* below). Placebo will comprise a similar looking inert saccharine tablet, administered four times per day. Ethically, the administration of placebo to early-onset PD sufferer's is not likely to be an issue as current therapy is withheld for as long as possible, as research has shown.

*2.Sample population and size:* Ideally, a large number of participants are desirable in order to reduce the incidence of random sampling error (Polgar & Thomas 2000, p.38). However, since this would be the first study of its kind, a smaller selection of participants may be more appropriate, resembling a pilot study (Polgar & Thomas 2000, p.30). A random representative sample comprising 40 participants of both male and female gender (age open) are recruited based on the following inclusion criteria:

(i) Clinical diagnosis of PD having been confirmed; and (ii) Signs and symptoms of disease to be short in duration and mild in severity, which do not affect social communications, daily life or work of the participant (Guohua 2008, p.39); and (iii) Modified Hoehn and Yahr grading not to exceed 1.5 (see below) (Guohua 2008, p.39); and (iv) Declaration that therapies, other interventions, drugs or alcohol are not currently used or intended to be used throughout study duration.

*3.Data collection methods:* The following tools are to be used at baseline and quarterly throughout the study for individual assessment and data collection:

(1) Berg Balance Scale (BBS), Forward Functional Reach Test (FFR), Backward Functional Reach Test (BFR), Timed "Up & Go" Test (TUG) and measures of gait speed to assess functional capabilities (Qutubuddin et al 2005, p.789; Brusse et al 2005, p.136). These are valid screening and ongoing assessment tools for PD sufferer's.

(2) 15D health related quality of life (HRQoL) instrument. Studies have shown this to be a valid, feasible and sensitive tool to assess quality of life in PD, especially related to disease progression affecting mobility, eating, speech and sexual functions (Haapaniemi et al 2004, p.976). Unlike the UPDRS (see below), HRQoL incorporates the patients' own perspective of their health and is considered by some to be a critical measure in health care (Schrag, Jahanshahi & Quinn 2000, p.308).

(3) Unified Parkinson's Disease Rating Scale (UPDRS) to assess severity of disease. Comprises six sections: I – Mentation (Mental Activity), Behaviour and Mood (4 questions); II – Activities of Daily Living (ADL) (13 questions); III – Motor Examination (14 questions); IV – Complications of Therapy (11 questions); V – The Modified Hoehn and Yahr Stage Scale*; and VI – The Schwab and England Activities of Daily Living Scale. A range of scores are given to represent "no impairment" through to "marked impairment" (Brusse et al 2005, p.135).

*Refer to Appendix 1 for supplemental information on the Hoehn and Yahr Stage Scale.

(4) Observation of subtle signs of PD such as reduced facial expressions, a lack of gestures, or a subtle tremor (Natural Standard 2009, p.3).

*4.Main variables being measured:* The hypothesis motivating the study is that components of *Vitex agnus-castus* are capable of crossing the BBB and exerting an effect on $D_2$ receptors, such that the symptoms and progression of PD are favourably altered or arrested. In measuring physiological capabilities with the aforementioned tools, it is hoped and expected that neither existing symptoms worsen, nor new symptoms arise whilst undergoing treatment with *V. agnus-castus*. Hence, the main variables being measured are the emergence (or sustained absence) of primary dopaminergic symptoms – tremor, rigidity, bradykinesia, impaired balance and coordination (Natural Standard 2009, p.2).

## Conclusion

Research has shown that contemporary orthodox treatment regimes addressing the symptoms of PD are ineffectual at best and detrimental at worst. Annual diagnoses of the disease are escalating with an ageing population and a breakthrough treatment is crucial in stemming the tide of disability and suffering endured by thousands. Herbal medicine is paving the way for novel and efficacious treatments, providing an integration of empirical and scientific data. Newly discovered pathophysiological mechanisms of remedies such as *V. agnus-castus* are opening up exciting avenues of exploration.

History tells us that *V. agnus-castus* is virtually devoid of side effects while science has revealed its affinity for dopamine receptors *in vitro*. Researchers are beginning to pose the question: "What if?" Some argue that increasing dopamine production is the key in treating PD; others imply that restoring receptor activity is the answer. If found ineffective as a sole treatment in PD, *V. agnus-castus* may yet prove a useful adjuvant in addressing the hypersexuality seen with some allopathic drug preparations, given its historical use in suppressing libido. Investigating if and how *V. agnus-castus* interacts with dopamine receptors in human models of PD will go part way in addressing the urgent need for effectual intervention.

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## Appendix 1

**Table 1:** ***Comparison between the original and modified Hoehn and Yahr scale***

| Hoehn and Yahr scale | Modified Hoehn and Yahr scale |
|---|---|
| 1: Unilateral involvement only, usually with minimal or no functional disability. | 1.0: Unilateral involvement only. |
| 2: Bilateral or midline involvement without impairment of balance. | 1.5: Unilateral and axial involvement. |
| 3: Bilateral disease: mild to moderate disability with impaired postural reflexes; physically independent. | 2.0: Bilateral involvement without impairment of balance. |
| 4: Severely disabling disease; still able to walk or stand unassisted. | 2.5: Mild bilateral disease with recovery on pull test. |
| 5: Confinement to bed or wheelchair unless aided. | 3.0: Mild to moderate bilateral disease; some postural instability; physically independent. |
| | 4.0: Severe disability; still able to walk or stand unassisted. |
| | 5.0: Wheelchair bound or bedridden unless aided. |

**Source:** *The Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease.*

http://www.movementdisorders.org/UserFiles/hoehnyahr.pdf