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Invited Review

A Review on the Possible Neuroprotective Effects of *Moringa Oleifera* Leaf Extract

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Summary: *Moringa oleifera* is an edible plant that has been reputed to be a miracle plant by numerous authors, with effects on practically every body system. Phytochemical analyses have demonstrated that the leaves are rich in various minerals, vitamins and antioxidants. Its use in some continents dates back to Antiquity. Neurodegeneration are chronic diseases of the nervous system. There is currently an increase in the use of natural products to combat these debilitating diseases. So far, no suitable cure has been found, and conditions are managed and the symptoms treated. This article reviews the literature on the effects of *Moringa oleifera* leaves on the nervous system in vivo and in vitro.

Keywords*: Moringa oleifera*, Neurodegeneration, Nervous system, Polyphenols

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INTRODUCTION

The use of herbs or plants to treat ailments still remains the most abundant, affordable, reliable, most trusted and well understood form of health care in a very good number of African villages (Abalaka *et al*., 2009; Awodele *et al*, 2012), since about 80% of the African population has been reported to use one form of traditional herbal medicine or the other (WHO, 2002). The development of orthodox medicine has somehow reduced the herbal health care system, but the development of resistance against orthodox medicine and the high cost and lack of availability has begun to make a lot of people go back to the use of herbal plants (Lee, 2006; Lam, 2007; Ogbunugafor *et al*., 2008), especially since they are generally considered safe.

Moringa oleifera is a medium sized tree in the family Moringaceae, consisting of a single genus Moringa. The family has been reported to have parietal placentation, 3-valved fruit and winged seeds. Different species ranging from four to ten has been reported by different people. *Moringa oleifera* leave is distinguished by its tripinnate leaves (Ramachandran *et al*., 1980). The plant is reportedly fast growing and drought resistant (Fuglie, 1999). It is an edible plant reportedly used in African and Asian countries as food and medicine for many centuries (Iqbal *et al*., 2006). The leaves are rich sources of potassium, calcium, phosphorus, iron, vitamins A, C and D, essential amino acids and antioxidants (vitamin C, β-carotene, flavonoids) (Bamishaiye *et al*., 2011). Also, other compounds like alkaloids, tannins, phenolics, saponins and steroids have also been reported to be present in the leaves (Sutalangka *et al*., 2013). Antioxidant activity has also been demonstrated in extracts of the leaves (Ijeomah *et al*., 2012; Sutalangka *et al*., 2013), higher than the other parts of the plant - the highest total phenolic content (105mg gallic acid equivalents/100 g), the highest total flavonoid content (31mg quercetin equivalents/100 g), and ascorbic acid content (107 mg/100 g) (Singh *et al*., 2009).

In spite of the presence of the defence mechanisms in the nervous system, the nervous system still remains susceptible and vulnerable to various dangers and damages, which are up to 600, already identified disorders (Giacoppo *et al*., 2015). With the study of neurodegenerative diseases, there is an increase in the discovery of new natural compounds possessing pharmacological activities. Consequently, a number of studies have shown that plant-derived chemical compounds have potential-health promoting abilities (Giacoppo *et al*., 2015). A wide variety of phytochemicals have been shown to prevent the risk of carcinogenesis and some chronic diseases like neurodegenerative diseases (Calabrese *et al*., 2012; Alrawaiq and Abdullah, 2014; Fuentes *et al*., 2015).

Neurodegenerative diseases are chronic diseases or disorders of the nervous system, having different aetiologies. Many are hereditary, some are secondary to toxic or metabolic processes, and others result from infections and trauma. Neuropathologically, these are chronic and progressive disorders characterized by the gradual loss of neurons in defined areas of the central nervous system. Alzheimer's disease, Parkinson's

disease, Huntington's disease, multiple sclerosis, amyotrophic lateral sclerosis, traumatic brain injury, spinal cord injury and cerebral ischemia/reperfusion are considered the disorders with the highest incidence in the population worldwide (Giacoppo *et al*., 2015). The mechanisms triggering neurodegeneration are largely unknown; although it has been suggested that oxidative stress plays a key role in its development (Calabrese *et al*., 2007). This has resulted in an increased interest in the use of natural compounds as a source of powerful and effective antioxidative agents in the treatment of these pathologies (Giacoppo *et al*., 2015).

The aim of this article is to review different studies on the effect of *Moringa oleifera* leave extracts and derivatives on the nervous system, *in vivo* and *in vitro*.

METHODOLOGY

Electronic search using www.pubmed.com yielded 15 articles (year of publication ranging from 2003 to 2016) when the search words *Moringa oleifera* and brain, were used. Five of these articles were on the effect of the leaves, while the remaining ten articles discussed the bark, seeds, roots, flowers and other derivative compounds. Using similar search words on www.scholar.google.com yielded 2, 570 (two thousand, five hundred and seventy) results, year of publication being from 1992 to 2016.

General Preparation of the Leave Extract

The *Moringa oleifera* leaves (MOL) are prepared in different ways before being administered to the animal subjects, the most favoured common laboratory rodents (rats and mice). The extracts vary from aqueous form (Ganguly *et al*., 2005; Adedapo *et al*., 2009), alcohol extracted form (Ganguly and Guha, 2008; Kirisattayakul *et al*., 2012; Sutalangka *et al*., 2013), to the air-dried and pulverised form (Nkwukwana *et al*., 2014). The alcohol extracted form seems to be the most widely used form of the extract, with the reported yield varying from 1.34% (Mohan *et al*., 2005), 10% (Ganguly and Guha, 2008), to 17.49% (Kirisattayakul *et al*., 2012; Sutalangka *et al*., 2013). Further analysis or fractionations by some authors (Verma *et al*., 2009; Rajanandh and Kavitha, 2010; Ogbunugafor *et al*., 2012; Vinoth *et al*., 2012; Berkovich *et al*., 2013), recorded the presence of flavonoids, phenolic compounds, vitamins and some amino acids. Extracts were normally administered per os.

Therapeutic potential, Toxicity studies and LD_{50} of MOL

Before the advent of orthodox medicine, Africans relied on herbs to care for health problems, while also using them as a source of food (Abalaka *et al*., 2009; Awodele *et al*, 2012). Many herbal medicines are believed to have preventive effects on chronic diseases due to their radical scavenging or antioxidative properties (Potterat, 1997). MOL has been shown to have a high level of phenolic contents, which have antioxidative effects. Many phenolic compounds display an antioxidative effect more potent than vitamin E in vitro and also inhibit lipid peroxidation by chain-breaking peroxyl-radical scavenging. They also directly scavenge reactive oxygen species like hydroxyl, superoxide and peroxynitrite radicals (Tsao and Akhtar, 2005); and to scavenge free radicals associated with 2, 2-diphenyl- 1-picrylhydrazyl (DPPH) radical, superoxide, and nitric oxide as well as to inhibit lipid peroxidation (Sreelatha and Padma, 2009). Polyphenols constitute the largest class of phytochemicals and dietary polyphenols have been shown to play important roles in human health (Ogbunugafor *et al*., 2012).

So far, only five studies on the use of MOL have been reportedly conducted and published in humans, using powdered whole leaf preparations. These publications demonstrated the anti-hyperglycemic (antidiabetic) and anti-dyslipidemic activities of MOL. No adverse effect was reported in these human studies (Stohs and Hartman, 2015). None of these human studies evaluated the effect on the nervous system.

Several animal studies have been conducted to assess the toxicity of various preparations of MOL and also the ideal dose, all giving varied results and values. Administering the aqueous extract, at doses of 400, 800, 1600 and 2000 mg/kg daily for 21 days (single acute dose at the highest dose) were deemed to be safe in rats, using indices such as blood cell counts and serum enzyme level, although a dose-dependent decline in body weight was observed (Adedapo *et al*., 2009). In 2011, Ambi *et al*., gave rats varying amounts of the powdered MOL incorporated into the feed, for 93 consecutive days. Observable lesions were reported in all organs, including the brain which reportedly showed neuronal degeneration and necrosis of glial cells. Concentrations of MOL used in this study were up to 75% of the feed. The reasons given for some of the pathologies observed were speculated to be probably due to the presence of some trace elements in the leaves, even though observed in the least detectable limits e.g. strontium (69± 3 ppm), rubidium (12 ± 2 ppm) and zirconium (11±2 ppm). The authors went further to caution against indiscriminate eating of large quantities of MOL in the area in which the study was carried out.

In another study by Asare *et al*., (2012), the aqueous extract of MOL were found to be genotoxic, based on blood analysis at 3000 mg/kg. This dose is higher than what is normally consumed in humans. A further assay by the same authors revealed cytotoxic effects at 20 mg/kg using human peripheral blood mononuclear cells in vitro.

Other authors have recorded very high doses of the aqueous extract in mice, and established the LD_{50}. Awodele *et al*. (2012) in an acute study administered 6400 mg/kg orally, and 1500 mg/kg intraperitoneally in an acute study. The same authors in a subchronic

study of 60 days, daily administered 250, 500 and 1500 mg/kg of the extract per os. The authors claimed no significant toxicity signs were observed, even with evaluation of haematological and biochemical parameters, except the dose-dependent reduced food consumption observed in the group treated with 1500 mg/kg. LD_{50} was estimated to be 1585 mg/kg. The oral dose appeared to be the safest form of administration of the extract.

The toxicological effects of the prolonged use of the alcoholic extract of MOL has also been documented by Bakre *et al*. (2013) and Oyagbemi *et al*. (2013). According to Bakre *et al*. (2013), the ethanolic extract of the leaves showed a significant dose-dependent decrease in rearing, grooming, head dips and locomotion; although they also reported an increased anxiogenic effect and enhanced learning. The authors concluded that the leaves possessed a CNS depressant and anticonvulsant properties, the action of which was possibly mediated through the enhancement of the central inhibitory mechanism. This probably justifies the use of the leaves to treat epilepsy in traditional medicine.

Oyagbemi *et al*. (2013) demonstrated that the chronic administration of the leaves may predispose the subject to hepatic and kidney damage.

MOL and Neurodegeneration

Derivatives of MOL that have been shown to be effective against neurodegeneration include glucosinolates. Glucosinolates and their breakdown products, isothiocyanates have been reported to be present in little amount in Moringaceae plants. (Galuppo *et al*., 2014; Giacoppo *et al*., 2015). In recent years, glucosinolates have attracted a lot of research interest due to their reported protective effect against neurodegeneration (Giacoppo *et al*., 2015). Some types of glucosinolates (R,S-Sulforaphane – SFN) have been reported to offer protection to mesencephalic dopaminergic neurons from cytotoxicity and oxidative stress by removing intracellular quinone products, prevent reactive oxygen species production, DNA fragmentation and membrane breakdown (Han *et al*., 2007). SFN also protected primary cortical neurons against injuries caused by the oxidized products of dopamine (Spencer *et al*., 2002; Vauzour *et al*., 2007).

Use of MOL and derivatives in *in vivo* studies

The hippocampus plays a vital role in the spatial memory (Parron *et al*., 2006), while the dorsal hippocampus provides animals with a spatial map of their environment. This it does by making use of reference and working memory (Liu and Bilkey, 2001). Lesions in this region cause problems relating to goal-directed navigation and also impair the ability to remember precise location (Herbert and Das, 2004). Mohan *et al*. (2005) reported the nootropic activity of MOL and so, the ability to improve memory in male and female rats. The leaves displayed a facilitatory effect on retention and acquired learning, using the passive shock avoidance test and elevated plus maze. The extract administered at 100 mg/kg significantly reduced the number of mistakes and latency time to reach the shock free zone. With the elevated plus maze, the extract at 50 mg/kg significantly reduced the transfer latency on the second day of testing, while also antagonising the effect of scopolamine.

In a previous study by Sutalangka *et al*. (2013), experimental rats were administered AF64A (a cholinotoxin) via the intracerebroventricular route, to induce dementia, administration of the alcoholic extract of MOL showed a significant reduction in the escape latency time when subjected to Morris water maze. Also, a corresponding increase in neuronal density of the CA1, CA2, CA3 and the dentate gyrus regions were also observed in groups administered the extract as a treatment to AF64A. The extract also significantly attenuated the decreased activities of superoxide dismutase and catalase induced by AF64A, and decreased malondialdehyde level.

Some compounds isolated from MOL have been shown to have protective effects on the components of the CNS. Protease inhibitors (proline and alanine) isolated from MOL was successfully used to alleviate the extent of axonal damage treat degenerating axons in rats induced with spinal cord injury resulting in paraplegia in the experimental rats. The protease inhibitors were administered intraperitoneally for the first three post-operative days. Recovery of some level of hind limb function was reported to be better in the drug-treated rats after 7 days post-operation. Quantitative analyses of secondary axonal degeneration at sites remote from the direct mechanical insult was reported to have provided solid evidence for the beneficial effects of protease inhibitors. In the rats treated with proline, the amount of degenerating axons was 13% less than that in untreated controls ($P < 0.001$), and a similar effect was observed in the rats treated with alanine at a dose of 500 mg/kg of body weight, the amount being 12% less than in untreated controls. These protease inhibitors however were said to not cross the blood brain barrier (Singh *et al*., 2012).

Kirisattayakul *et al*. (2012; 2013) demonstrated the potential benefit of the hydroalcohol MOL extract in decreasing brain infarct volume, and also its neuroprotective effect against focal cerebral ischemia. Ischemic stroke was induced by occlusion of the middle cerebral artery, and the animals were fed extract of MOL. Results showed cerebroprotective effect and enhanced superoxide dismutase activity in the hippocampus, and decreased malondialdehyde levels in cerebral cortex, hippocampus and the striatum.

Use in neuronal cell culture

MOL has been used in ayurvedic medicine to treat a number of central nervous system (CNS) ailments, ranging from paralysis, nervous debility to nerve

disorders (Hannan *et al*., 2014). There has been evidence for nootropic and neuroprotective disorders in cell cultures of neural cells and in animal models (Hannan *et al*., 2014). Using hippocampal neurons, Hannan *et al*., (2014) reported that the addition of MOL ethanolic extract significantly increased the number and length of neurites and their branching, in a dose-dependent manner, with the optimal concentration achieved at 30 µg/ml. In the same experiment, neuronal viability was increased, cellular injury was decreased and the rate of neuronal differentiation was also accelerated. No cytotoxicity was observed. Neurons also exhibited more extended and multiple branching, an increase in the number and length of primary dendrites and also the appearance of more secondary and even tertiary dendrites. MOL was also observed to modulate axonal development and promote synaptogenesis. The reasons for this multiple branching and differentiation observed could be due to the presence of β-carotene, which is abundant in MOL. β-carotene has been reported to be an inducer of neuronal cell differentiation (Lee *et al*., 2013).

CONCLUSION

The mechanism of action of *Moringa oleifera* leaves is probably due to the high level of polyphenols and other antioxidative compounds it possesses, which confer neuroprotection by scavenging free radicals or activating cellular antioxidant system (Luqman *et al*., 2012). There is an abundance of data on the use of MOL to treat conditions relating to diabetes, hyperlipidemia, hypertension, hypoglycaemia and some other related conditions, but currently very little information on pure compounds derived from MOL which have been successfully used to treat neurodegeneration, neurological or related conditions. The current economic recession being experienced world-wide, especially in African countries, is likely to make people seek out the use of herbal medicine more, thereby necessitating the need for further research on this plant. Further investigation still needs to be carried out to isolate and determine a compound that is ideal for combating neurodegeneration.

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