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Madhuca longifolia and saxagliptin combination approach in neurodegenerative diseases: A review

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Abstract
Neurodegenerative disorders (ND) are the universal and most widespread cause of fatal situations worldwide, especially in the older population. The present aimed to review the possible potential of herbal and antidiabetic therapy for such neurodegenerative diseases. The literature search for the review was achieved from PubMed, Google Scholar, Science Direct to recollect relevant articles. The purpose of the literature search was to obtain potential evidence of *Madhuca longifolia* and antidiabetic drugs in the management of neurodegenerative disease from 2003 to 2021. Here we reviewed and found that herbal drugs (M. longifolia) and antidiabetic drugs combination could work by boosting the potential of each other and might have a potential benefit.

Keywords: *Madhuca longifolia*, antidiabetic drug, combination treatment, neurodegeneration, neurodegenerative diseases

Introduction
Neurodegenerative disorders (ND) are the universal and most widespread cause of fatal situations worldwide, especially in the older population. The victims of neurodegeneration suffer from several clinical manifestations [1]. Neurodegeneration and associated diseases are the major health burdens on the population globally. The major three neurodegenerative diseases are Parkinson's disease (PD), Alzheimer's disease (AD), Amyotrophic lateral sclerosis (ALS). AD affects roughly 30% of the population among 85 years [2]. These three deadly diseases affected nearly 20 million population globally [3]. AD, PD and ALS reveal two major common features, one is the occurrence intensify with age and another is it is commonly reported as sporadic cases with frequent age of outbreak below age 50 [4]. The pathophysiology behind the neurodegenerative diseases is considered to be an accumulation of specific proteins, autonomic dysfunction. However, neurodegenerative diseases reveal many intricate harms linked with progressive neurodegeneration and neuronal death, like proteotoxic stress, oxidative stress, neuroinflammation, programmed cell death, and abnormalities in autophagosomal/ lysosomal and ubiquitin proteasomal system [5]. Neurodegenerative conditions (AD, PD, ALS) might become deadly in future and global challenges for public health and medicine worldwide. The present review aims to address the possible potential of herbal and antidiabetic drug in neuroprotection.

Materials and Methods
The literature search for the review was achieved from PubMed, Google scholar, Science direct to recollect relevant articles. The purpose of the literature search was to obtain potential evidence of *Madhuca longifolia* and antidiabetic drugs in the management of neurodegenerative disease from 2003 to 2021. The search terms included epidemiology of neurodegenerative diseases, *Madhuca longifolia* in the treatment of neurodegeneration, *Madhuca longifolia* in the treatment of PD, antidiabetics in the treatment of neurodegenerative diseases, Saxagliptin in the treatment of neurodegeneration, antidiabetic in the treatment of PD, antidiabetic in the treatment of AD, *Madhuca longifolia* antioxidant, anti-inflammatory potential, M longifolia in the treatment of epilepsy, *Madhuca longifolia* associated suppression of inflammation, Saxagliptin as a novel anti-PD.

Medical potential of *Madhuca longifolia:* Simon *et al*. investigated and evaluated the

beneficial effect of *Madhuca longifolia* (aqueous leaf extract) against diclofenac-induced toxicity. The extract was orally induced to rats in different doses The hepatic proinflammatory mediator cytokines like interleukin (IL) IL-6, IL-1β and TNF-α, were evaluated through Enzyme-Linked Immunosorbent Assay (ELISA). Western blotting techniques were used to assess the protein expression of Caspase-3, Cyclooxygenase (COX-2), and NF-κB. Aqueous leaf extract of M. longifolia was able to normalize the changes caused by diclofenac [6]. Similarly, Prince *et al*. reported the protective effect of aqueous leaf extract of *Madhuca longifolia* through suppression of inflammation, oxidative stress and cytokine formation in Diclofenac-induced renal toxicity in female Wistar albino rats. The cytokines like IL-6, IL-1β and TNF-α were assessed by ELISA techniques and the concentration of NF-κB, Caspase-3, and COX-2 were measured through western blotting techniques. M. longifolia has revealed potential against toxic effects caused by diclofenac. The significant result of the aqueous leaf extract of *Madhuca longifolia* was due to its ability to restore renal function by restoring antioxidants and preventing cellular damage [7]. Patel *et al*. studied the anticonvulsant activity of heartwood extract of *Madhuca longifolia* and the possible mechanism of action involved in this activity. Pentylenetetrazole (PTZ) is used to induce seizures in mice. Additionally, Benzodiazepine (BZD) is taken as a standard drug to induce the convulsants. The heartwood of *Madhuca longifolia* (methanol extract) revealed potential against convulsions. This result reported that M. longifolia has a biologically active component which has the potential to recover from convulsions. This supports the ethnomedical claims of the use of plants in the management of epilepsy [8]. Additionally, Agraval *et al*. in their comparative study reported antioxidant properties of the Terminalia paniculata and M.longifolia (methanolic extracts). The *in vitro* methods revealed the antioxidant properties and free radical scavenging potential. The individual and combination of both extracts reported significant antioxidant properties. However, 2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS), 2,2-diphenyl-1-picrylhydrazyl (DPPH), and hydrogen peroxide (H2O2) radical scavenging potential was reported by M. longifolia and T. Paniculata potential was associated with intense scavenging potency in the case of nitric oxide and hydroxyl radicals [9]. Dambhare *et al*. reviewed the various ethnomedical and traditional uses of the bark and leaves of M. longifolia. Ethnomedical uses include significant anti-pregestational, antitumor, antipyretic, anti-inflammatory, hepatoprotective, antiestrogenic and wound healing potential. Traditionally bark of M. longifolia is used in ulcers, rheumatism, and tonsillitis and as an anticoagulant [10]. Singh *et al*. evaluated *Madhuca longifolia* embedded silver nanoparticles attenuate diethylnitrosamine (DEN)-induced renal cancer via regulating oxidative stress. Animals were grouped into five groups and administered with measured doses of silver nanoparticles for 16 weeks. Evidence revealed a dose-dependent antineoplastic effect in renal cancer when compared to DEN induced group. Significant changes were observed in biochemical parameters and dose-graded improvements in the level of antioxidant parameters were accountable for its protective nature. Silver nanoparticles in dose dose-dependent manner were effective in modifying the raised levels of pro-inflammatory cytokines and inflammatory mediators during renal cancer. However, renal histopath findings were suggestive of a few negative alterations which were associated with silver nanoparticle treated groups and considered. Bio Fabricated silver nanoparticles (MLAgNPs) using *Madhuca longifolia* can convey significant chemo-protective effect against renal carcinomas by halting the IL-1β, IL-6, and TNF-α utilizing nuclear factor-kappa B (NF-κB) pathway [11].

Simon *et al*. studied the Ameliorative activity of aqueous leaf extract from *Madhuca longifolia* against diclofenac-administered toxicity on rat stomach and intestine. Animals totalling thirty animals were segregated into five groups. Group I was considered as normal control, Group II was administered with diclofenac, Group III was administered with diclofenac and M. longifolia leaf extract, Group IV treated with silymarin and diclofenac, and Group V was administered with M. longifolia leaf extract alone. At the end of the study, anesthesia was administered and sacrificed to assess levels of cytokine, antioxidants, protein expression and histopathological alterations. Diclofenac-administered animals had significant ($p< 0.05$) alterations in cytokine, antioxidants, protein expression and pathological alterations as compared to rats administered with M. longifolia. This study demonstrated that *Madhuca longifolia* leaf extract had gastroprotective activity in rats treated with diclofenac [12].

Tables

The table should be made as simple as possible. Only a few horizontal lines should be used without vertical lines in the table. All tables should be placed after references in the manuscript. Each table should be consecutively numbered in Arabic numerals with a self-descriptive heading and/or legend. Any abbreviation or symbol used in the table should be described in the legend. The same data should not be represented in tables and in graphs.

Table 1: Reason for neuroprotective potential of M. longifolia observed in studies

Author	Findings/ outcome	Reference
Simon *et al*.	*M. longifolia* was able to normalize the changes (IL-6, IL-1β and TNF-α, Caspase-3, COX-2, and NF-κB caused by diclofenac.	[6]
Prince *et al*.	Aqueous leaf extract of *Madhuca longifolia* was due to its ability to restore renal function by restoring antioxidants and preventing cellular damage.	[7]
Patel *et al*.	*M. longifolia* has a biologically active component which has the potential to recover from convulsions.	[8]
Agraval *et al*.	ABTS, DPPH, and hydrogen peroxide (H_2O_2) radical scavenging potential were reported by *M. longifolia* and *T. Paniculata* potential was associated with intense scavenging potency in the case of nitric oxide and hydroxyl radicals.	[9]
Dambhare *et al*.	M. longifolia is used in ulcers, rheumatism, tonsillitis and as an anticoagulant.	[10]
Singh *et al*.	Bio Fabricated silver nanoparticles (MLAgNPs) using *Madhuca longifolia* can convey significant chemo-protective effect against renal carcinomas by halting the IL-1β, IL-6, and TNF-α employing nuclear factor-kappa B (NF-κB) pathway.	[11]
Simon *et al*.	*Madhuca longifolia* leaf extract had gastroprotective activity in rats treated with diclofenac.	[12]

Neuroprotective potential of Saxagliptin: Literature-based hypothesis

Solini *et al*. assessed the vascular effects of chronic administration of saxagliptin (Saxa) in db/db mice, a model of type 2 diabetes, evaluating vascular structure and endothelial function in mesenteric small arteries to explore the hypothesis that Dipeptidyl Peptidase-4 (DPP-IV) is involved in the diabetes-induced vascular damage. Saxa was relatively sensitive to restoring the repression of N^G-Nitro-L-arginine methyl ester (L-NAME) and ameliorating acetylcholine-induced relaxation. Additionally, by L-NAME and Saxa attenuated, Dihydroethidium associated increased intravascular superoxide production in db/db. Moreover, Saxa restored the dimer/monomer proportion of endothelial Nitrous oxides (NOS) which was hampered in db/db mice. Saxa reverses vascular hypertrophic remodeling and ameliorates NO availability in small arteries from db/db mice through the abrogation of NA(P)H oxidase-driven NOS uncoupling and by reducing the action of cyclooxygenase-1-derived vasoconstrictors downregulating the expression of thromboxane-proteinoid receptors [13].

Saleh *et al*. worked on "Neuroprotective outcome of saxagliptin against scopolamine-induced Alzheimer's-resembling pathology in rats". The researcher investigated the probable role of neuronal insulin signalling cascade and its interaction with cholinergic and gamma-aminobutyric acid (GABAergic) systems as possible mechanisms by which saxagliptin protects against scopolamine-induced Alzheimer (AD)-like pathology in adult male rats. AD-associated pathology was induced by an everyday intraperitoneal injection of scopolamine at a dose of 3mg/kg for six weeks. Animals were administered orally with saxagliptin, one hour before scopolamine injection, at a dose of 3mg/kg for six weeks. Saxagliptin recovered scopolamine-induced impairment of neuronal insulin. together, the outcome suggests that saxagliptin can have a hopeful therapeutic effect in mitigating scopolamine-induced interruption of insulin signaling and other pathological aberrations in Alzheimer's disease [14]. Nassar *et al*. reported saxagliptin could potentially improve motor functions and muscle coordination along with correction of akinesia in the rotenone model. Additionally, saxagliptin safeguarded substantia nigra pars compacta thyroxine hydroxylase (SNPCTH) immunoreactivity. Additionally, saxagliptin decreased tyrosine hydroxylase (TH) in the striatum, complex I and dopamine (DA). Saxagliptin is also protected from rotenone-associated intensified striatal DPP-4 and hampered adenosine triphosphate/adenosine diaphosphate (ATP/ADP), cyclic adenosine monophosphate (cAMP) and brain-derived neurotrophic factor (BDNF). Additionally, saxagliptin revealed potential against inflammation, saxagliptin could significantly decrease rotenone-associated increased neurotrophic factor levels [15].

Table 2: Reason for neuroprotective potential of saxagliptin observed in studies

Author	Findings/ outcome	Reference no.
Solini *et al*.	Saxa reverses vascular hypertrophic remodelling and ameliorates NO availability in small arteries from db/db mice through the abrogation of NA(P)H oxidase-driven eNOS uncoupling and by reducing the action of cyclooxygenase-1-derived vasoconstrictors downregulating the expression of thromboxane-prostanoid receptors.	[13]
Saleh *et al*.	Saxagliptin can have a hopeful therapeutic effect in mitigating scopolamine-induced interruption of insulin signalling and other pathological aberrations in Alzheimer's disease.	[14]
Nassar *et al*.	Saxagliptin revealed potential against inflammation, saxagliptin could significantly decrease Rotenone-associated increased neurotrophic factor levels.	[15]

Conclusion

The research on potential therapies to manage deadly neurodegenerative diseases is the need of the day. Here we reviewed and found that herbal drugs (M. longifolia) and antidiabetic drugs combination could work by boosting the potential of each other and might have a potential benefit in controlling neurodegeneration

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