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Research Article

Ethnomedicine and Neuroscience in the developing world: plants most commonly used for neurological conditions

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Abstract
The use of plants for curing ailments in humans and animals has been an ancient practice. African medicinal plants have been used to cure various types of disease conditions. Ethnomedicine has been proposed to be a very promising area that is capable of adding value to the very rich natural resources of the African continent. Recently, there seems to be a re-awakening of interest in the use of medicinal plants especially in Africa with the outbreak of the coronavirus pandemic. Medicinal plants can be defined as vegetables containing substances utilized for therapeutic purposes. They can be processed through different physical or biological processes, such as *extraction*, fractionation, purification, and concentration, to enhance usage. Most African countries are growing economies, where the Gross Domestic Product (GDP) of the populace is very low, leading to low purchasing power, thus resulting in the populace depending on alternative medicine by using their traditional and indigenous plants for the remedies of various ailments. The potentials of some medicinal plants as treatments for certain neurological conditions are an interesting area in neuroscience research in Africa. A significant number of researches have been carried out in the field of neuroscience to analyse the therapeutic potential of some plants mostly domiciled on the Africa continent. This review therefore attempts to harvest this information and present it in a concise form for global appreciation of the potential in Africa's ethnomedicine, with a focus on five common plants (*Telfairia occidentalis, Garcinia Kola, Ocimum gratissimum, Moringa oleifera, Nigella sativa*).

Key Words: African medicinal plants, neuroscience, alternative medicine, neurological conditions

INTRODUCTION

Ethnomedicine, sometimes used as a synonym for traditional or indigenous medicine is an area of medicine that refers to the health beliefs of people, their knowledge and common practices derived from indigenous cultural use of medicinal plants. Ethnomedicine can be considered as a medical system that studies different societal notions and cultural concepts of health, disease, illness, and wellness, including the nature of local healing systems and their knowledge about natural remedies (Teixidor-Toneu *et al*., 2016). A number of diverse indigenous plants which have been known to be remarkably relevant in the treatment of ailments have been found to grow abundantly in Africa. From times immemorial, the African and Asian fore-fathers have used plant leaves, bark, stem and roots to ameliorate different health conditions. In more recent times, there has been an increasing demand for medicinal plants (Dzoyem *et al*., 2013). There is a rich variety of plants reported to have been used in traditional medicine, and reputed to possess protective, preventive and therapeutic properties (Mahomoodally, 2013). Plants are believed to be a readily available source of new substances or molecules and are therefore useful in the formulation of new and improved drugs in the health and pharmaceutical company (Shah *et al*., 2006). Traditionally, medicinal plants have been used in the African continent as a therapeutic resource for health care, and have served as materials for drug discovery and synthesis (Sofowora, 1993). The World Health Organization (WHO, 2008) described medicinal plant as a plant that has one or more of its parts (bark, leaves, and stem) which contains substances that is used for the production and synthesis of drugs. This definition differentiates the plants with therapeutic properties, whose constituents have been scientifically proven, from plants that are also regarded as medicinal, but are yet to be subjected to thorough scientific investigations. Medicinal plants have also been described as herbal preparations or herbal drug, such as whole plant, or plant parts produced by subjecting plant materials to physical or biological processes such as extraction, fractionation, purification, and concentration produced for consumption as herbal products (Abubakar and Haque, 2020). Several plants known to possess

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curative, protective and preventive properties are widely used in traditional medicine. They are known to cure diseases affecting various organs including the nervous system (Shah *et al*., 2006).

Neuroscience is an important discipline in biomedical research due to the involvement of the study of the nervous system in the coordination of both conscious and unconscious body organs (Karikari *et al*., 2016). The nervous system is endowed with different defence mechanisms, but in spite of this, it still remains vulnerable and susceptible to various damages and disorders (Giacoppo *et al*., 2015). The increase in awareness and study of neurological conditions and possible therapeutic interventions have resulted in an increase in the research and discovery of some new and natural compounds which possess neuro-pharmacological related activities. This has resulted in the discovery of chemical compounds from plant origin with potential neuroprotective and health promoting abilities (Giacoppo *et al*., 2015). Researchers have reported the potentials of several phytochemicals in preventing and curing neurological diseases (Calabrese *et al*., 2012; Alrawaiq and Abdullah 2014; Fuentes *et al*., 2015). Recently, researchers have begun to show interest in the use of plants and their derivatives to combat neurological diseases.

This review focuses on five common plants (*Telfairia occidentalis, Garcinia Kola, Ocimum gratissimum, Moringa oleifera, Nigella sativa*) documented benefits in treating/ameliorating neurological conditions both in vitro and in vivo. Particular emphasis on the mechanism of action and effects of these plants on the nervous system were also documented. The authors hope to bring together the unique neurological attributes of some plants.

MATERIALS AND METHODS

A systematic review of the literature was conducted to retrieve studies published and indexed in MEDLINE (PubMed), Google scholar and in Scopus databases using the following key words: selected plants, brain, neuroscience, in vitro and in vivo studies, pathology and pathogenesis. The inclusion criteria were plant extracts, different plant parts, protective and ameliorative studies, neurological studies, neuro-pathologies and experimental studies, all published in English. Exclusion criteria were studies that were not original, field studies, studies lacking adequate data and studies with non-representative samples. A total of 250 selected articles published since the 1990s were selected as being relevant based on the information provided in the titles and abstracts. According to the pre-established inclusion and exclusion criteria, a total of 98 articles were selected for in-depth evaluation in this review.

RESULTS AND DISCUSSION

***Telfairia occidentalis*:** *Telfairia occidentalis* (TO), a regularly consumed vegetable of importance is cultivated in Nigeria, and eaten as a leafy vegetable. It belong to division; Tracheophyta, subdivision; Spermatophytina, class; Magnoliopsida, family; Cucurbitaceae, genus; Telfairia Hook and species *Telfairia occidentalis* Hook. f. – fluted gourd. It is commonly referred to as fluted gourd or fluted pumpkin. It has different local names in the different dialects of Nigeria including Aporoko or Iroko in Yoruba, ugwu in Ibo, Umee in Urhobo Ikong-ubong in Efik, and Umeke in Edo (Owoeye and Gabriel, 2016). The plant grows luxuriant green leafy vegetables rich in protein, carbohydrate, and minerals such as iron, calcium, potassium, phosphorus, sodium, including antioxidants (vitamins A, C, E). *Telfairia occidentalis* has been proven to have protective effects on the brain by virtue of its antioxidant property. Mercury intoxication in rat has been observed to cause damages to various organs including the brain via oxidative stress (Owoeye and Gabriel, 2016). Oral administration of TO aqueous extract was observed to have reversed the neurotoxic effects of mercury chloride on the brain. Mercury chloride (HgCl2) has been observed to induce oxidative and histological changes in the microanatomy of the brain which could be prevented by aqueous extract of TO. Some deleterious effects of HgCl2 such as death of the granule and purkinje cells of the cerebellum as well as pyramidal cells of the hippocampus have been documented. Owoeye and Gabriel (2016) observed that there were elevation of the malondialdehyde (MDA) level, catalase (CAT) and super oxide dismutase (SOD) activities, but reduced glutathione (GSH) levels which were all reversed by administration of the aqueous extract. The ameliorative changes observed in the groups treated with aqueous extract of TO suggests the potency of the antioxidant potential of this plant as well as its associated capacity to protect the hippocampus and cerebellum. Kayode *et al*., (2009) observed that TO ameliorated oxidative brain damage induced by protein malnutrition in experimental rats. The malnourished rats showed a decreased activity of SOD, CAT and MDA which were indicative of lipid peroxidation and increased presence of reactive oxygen species. Treatment with protein repletion in conjunction with TO extract resulted in a decrease in the level of oxidative brain damage in comparison with the group treated with protein repletion alone. The authors concluded that protein supplementation with TO was more effective in reversing the oxidative damage the brain suffered when compared to rats that received protein di*et al*one in the protein energy malnourished rat. The inhibitory effect of *Telfairia occidentalis* was investigated on acetylcholineesterase, butyl cholinesterase and lipid peroxidation induced by some pro-oxidants in the rat brain TO inhibited the activities of these enzymes as well as the lipid peroxidation which was induced by pro-oxidants in a dose dependent manner, this they observed was achievable through the prevention of the breaking down of acetylcholine which consequently increased the acetylcholine concentration leading to an increase in communication between the nerve cells (dependent on acetylcholine as a chemical messenger) (Oboh *et al*., 2011). The aqueous extract of TO administered per os was observed to have a reversal effect on irradiation-induced oxidative damage on the rat brain. Irradiation of rats with 2Gys of gamma rays (rats were observed for 24 hours and sacrificed, after 15 and 30 days post-irradiation). The rats treated with irradiation had significant increase in the levels of malondialdehyde, hydrogen peroxide and decreased levels of superoxide dismutase and glutathione. However, following treatment with TO the antioxidants' level became normal. Therefore, TO have protective effect against irradiation-induced oxidative stress in the brain (Adejuwon *et al*., 2014). Antioxidants may have interfered with the oxidation process in multiple ways, some of which may include but not limited to reacting with free radicals, acting as oxygen scavengers preventing lipid auto-oxidation and chelating catalytic metals. Therefore, the extracts of TO could be used in the treatment of

certain neurological conditions associated with reactive oxygen species. We observed that very few studies have been done on the effects of *Telfairia occidentalis* on the brain, however, its antioxidant ability maybe due to its high flavonoid content (Kayode and Kayode, 2011). Therefore, there is need for more research into the bioactivities of TO leaves and its extracts on the brain tissue.

***Garcinia Kola*:** *Garcinia Kola* (GK) seeds (nut), popularly known as bitter kola, belonging to the family *Guttiferae*, is widely distributed in moist forests in West and Central Africa. All of the plant parts, including the leaf, stem, bark, nut and root, are believed to be useful for the treatment of all sorts of ailments, in addition to being used as a poison antidote by traditionalists. However, the seeds are the most popularly used. GK seed is reputed to be high in antioxidants, with its constituents including biflavonoids, flavonoids, xanthones, and, terpenoids, phenols, saponins and benzophenones (Iwu, 1993; Igado *et al*., 2012). Different parts of the plant have different concentrations of the aforementioned phytochemicals (Okechukwu *et al*., 2013; Maňourová *et al*., 2019). In terms of nutritional composition, the plant contains reducing sugars, crude proteins, crude fibres, minerals and vitamins A, C, E, B1, B2 and B3 (Tcheghebe *et al*., 2016). Some reported pharmacological effects of the plants, particularly the seeds, include bronchodilator effects, anti-inflammatory, antiviral, antihepatotoxic and antidiabetic properties. It has also been reported to enhance brain function and ameliorate neurotoxicity (Iwu *et al*., 2002; Igado *et al*., 2012).

In another study, it was found that FeSO4-induced lipid peroxidation was inhibited by the methanolic leaf extract of GK in a dose-dependent fashion, with half maximal inhibitory concentration. A reaction of ferric Ethylenediamine tetra acetic acid (EDTA), hydrogen peroxide, ascorbic acid and deoxyribose was performed on certain homogenates of the brains of Wistar rats and hydroxyl radicals were produced in the reaction. These radicals are known to cause cell membrane damage by initiating a peroxidation of the lipid components of the cell membrane (Morsy, 2012). In a subsequent study, streptozotocin (a naturally occurring alkylating antineoplastic substance known to be toxic to the beta cells of the pancreas) was administered for 8 months followed by the oral administration of GK aqueous suspension for 30 days. Results obtained showed that GK conferred a level of neuroprotection on the brain, evidenced by the observed decreased neuro-inflammation and decreased neurodegeneration. (Farahna *et al*., 2017).

Garcinia Kola contains a potent bioflavonoid, kolaviron, which has been documented to exhibit admirable anti-oxidative ability (Farombi and Nwaokeafor, 2005; Igado *et al*., 2012). Blakemore and Franklin (2008) and Olajide *et al* (2016) demonstrated the role of kolaviron in ameliorating hippocampal damage, neurodegeneration and neurobehavioural deficits caused by the administration of cuprizone (a copper chelator neurotoxicant used to induce demyelination in experimental models of multiple sclerosis).

In another report, *Garcinia Kola* seeds (crushed and dissolved in water) and kolaviron, both administered per os, were used to treat vanadium-induced neuro-degeneration (Igado *et al*., 2012). Vanadium, a metal of the transition series, is an environmental pollutant that causes demyelination, neurodegeneration, lipid peroxidation and increased accumulation of reactive oxygen species (ROS) (Igado *et al*., 2018). *Garcinia Kola* administered at 100 mg/kg did not give a satisfying neuroprotection against vanadium administered at 1.5 mg/kg to experimental rats, but gave adequate protection when used with vanadium at 1.25 mg/kg. Histopathological and biochemical evaluations showed that although GK protected against the vanadium-induced neurotoxicity, kolaviron (100 mg/kg) gave a better protection. This is probably due to the fact that kolaviron is a purer compound that the GK seed (Igado *et al*., 2012).

Kolaviron treatment has also been reported to reduce neurodegeneration when administered before or after sodium azide (NaN3) treatment. Sodium azide causes lipid peroxidation at the mitochondrial membrane, resulting in increased permeability, leading to the release of intramitochondrial hydrogen peroxide and calcium which further facilitates inflow of calcium from extracellular sources. Due to the high lipid contents of neuronal membranes, reactive oxygen species production often leads to severe damage and neuronal cell death (Olajide *et al*., 2016).

Other reports of neuroprotection exhibited by kolaviron include:

- Protection against the effects of ɣ-radiation. This neuroprotective effect made the authors to suggest the use of GK seeds in moderation, to patients undergoing radiotherapy (Ahidjo *et al*., 2021).
- To ameliorate the spontaneous alternation deficits suggestive of cognitive impairments by scopolamine injection (Ishola *et al*., 2016).
- Co-administered with vitamin E, was effective in the reduction of phenytoin-induced oxidative stress in pubertal male rats (Owoeye *et al*., 2014).
- Reversal of striatal neuronal damage in rotenone-exposed rats (Farombi *et al*., 2019). Rotenone has been used to mimic Parkinson's disease in experimental conditions.

***Ocimum gratissimum*:** *Ocimum gratissimum* (OG) commonly known as scent leaf, is traditionally used for the treatment of anxiety, nerve pain, convulsions, angina headaches, psychiatric disorders and a variety of neurodegenerative disorders (Bora *et al*., 2011). The plant has been reported to exhibit antioxidant, anti-inflammatory and antimutagenic properties which enable it to carry out most of its functions in the brain (Lukamanul *et al*., 2008). The plant has been used to ameliorate damage associated with cerebral ischemia due to its antioxidative properties. Ischemia and associated oxidative stress cause increase neuronal death. An investigation of the potential protective effects of ethanol extracts of OG on the brain of Wistar rats revealed that associated brain stress and neurological disorders were significantly attenuated by pre-treatment through oral administration of ethanol extract of OG (Bora *et al*., 2010).

Alzheimer's disease is a progressive neurodegenerative disease associated with exposure to stress. The effectiveness of OG oil has been shown to improve the neurodegenerative changes induced in mice exposed to chronic unpredictable mild stress (Nasra *et al*., 2018). The findings showed that OG diminished depressive state, impaired short-term memory, up regulated the serum corticosterone level, hippocampal protein level, and brain derived neurotropic factor (Nasra *et al*., 2018). The brain is known to be vulnerable to oxidative injury due to its high oxidative metabolic activity and the related non-replicating nature of neuronal cells (Gupta *et al*., 2003). Free

radicals contribute to the development of neurodegenerative disorders; OG has been reported to display high chelating, free radical scavenging and antioxidant properties. The brain and nervous system generally, are particularly vulnerable to oxidative stress, which is related to the limited antioxidant generating capacity of the nervous system (Oboh, 2008). Free radicals in the brain lead to cell deterioration and are accountable for neurodegenerative disorders such as Alzheimer's disease, Huntington's disease, and Parkinson's disease (Gandhi and Abramov, 2012). The leaf extract of OG modulate neurodegenerative changes caused by a high concentration of lead acetate in the blood of Wistar rats. Stressed cells cause glutathione to be oxidized which in turn bind to lead making it unavailable as an antioxidant, however, OG balances the ratio by reducing lead and preserving reduced glutathione (Olayinka *et al*., 2011). High tissue levels of copper and iron with low tissue levels of magnesium and zinc play a huge role in brain degeneration and cancer (Johnson, 2001). Iron initiates lipid peroxidation and increases malondialdehyde (MDA) in the brain, although raised levels have been reported to be associated with Parkinson's disease (Faucheux *et al*., 2003). However, phenolic extracts of OG initiate a dose-dependent decrease in the MDA level in the brain. Phenolic extracts also scavenge nitric oxide to inhibit lipid peroxidation in a dose dependent manner exhibiting the high chelating properties of OG.

The hydromethanolic leaf extract of OG scavenges ROS and glycosides; and probably exerts its antioxidant effects in aiding learning and memory by reducing apoptosis, inhibiting membrane lipid peroxidation, promoting anti-inflammation, and amyloid β aggregation. The end results of these include are; an increase in blood-brain circulation and neurogenesis, and an improvement in neuroplasticity as well as the immune system (Stackman *et al*., 2003; Luo, 2006; Abiola *et al*., 2018). In vitro and in vivo studies have confirmed the anti-amnesic effects of OG (Singh *et al*., 2016), ameliorating some dementia-like pathologies. The alcoholic extract of OG reduced ischemia and infarct volume, implying that it has the potential to prevent stroke as well as combat its harmful effects (Bora *et al*., 2011; Abiola *et al*., 2018, 2020).

OG is rich in flavonoids, an antioxidant; documented to inhibit neuroinflammation, possess neuroprotective properties and also delay neurodegeneration (Spencer *et al*., 2012). The management of seizures induced by Pentylenetetrazol (PTZ) in laboratory animals is the principal protocol used in the characterization of a potential anticonvulsant drug therapy. The extract blocked tonic convulsions induced by Maximal Electroshock Seizure (MES) (Freire *et al*., 2006). There are always two sides to a coin; some negative effects have been documented on OG. A study showed the neurotoxic effect of OG on prefrontal cortical neurons of adult male Wistar rats that were administered high concentrations of 300 – 400 mg/kg OG (Ajibola *et al*., 2015). Acute use of this extract caused neuronal fragmentation and central chromatolysis of the nissl bodies in the cell body of a neuron with increases in cerebral acid phosphatase (ACP) and alkaline phosphatase (ALP) which are responses to axonal injuries leading to onset of neurodegenerative disorder affecting cognitive and executive functions of the prefrontal cortex (Ajibola *et al*., 2015). OG, thus causes apoptosis and depression of the central nervous system in a dose-dependent manner. However, on continuous administration, it invoked an inflammatory response that transited from acute to chronic. The reported toxicity is dose dependent and the extract is better tolerated orally than intra-peritoneally (Orafidiya, 2004). Reports by Lahlou *et al*., (2004) also showed that the intravenous administration of the OG oil resulted in immediate and significant bradycardia and hypotension, which were probably due to the presence of eugenol, a major constituent of OG oil.

***Moringa oleifera*:** *Moringa oleifera* (MO) is a small to medium sized multipurpose plant from the family *Moringaceae* and genus *Moringa* (Kirisattayakul *et al*., 2013). Originally, the plant is native to Asian countries but can be found in Africa and other tropical parts of the world due to its fast growing and drought resistant nature (Giacoppo *et al*., 2015). The family Moringaceae have been known to have parietal placentation, 3-valved fruits and winged seeds and it can be described as a perennial plant with spirally arranged leaves, whitish flower and low-quality timber (Fuglie, 1999). MO is known by numerous nomenclatures such as marango, miracle tree, ben oil tree, magic tree, benzolive, "Saijan" (Hindi), "Kelor" (Malaysia), "Zogalegandi" (Hausa), "Okweoyibo" (Igbo) and "Ewe igbale" (Yoruba), but it is commonly and popularly known as Horse-radish tree or Drumstick tree (Owolabi *et al*., 2012). According to many authors, MO is an edible plant that has both nutritional and medicinal properties (Stohs and Hartman, 2015; Igado and Olopade, 2016). MO has an impressive wide range of medicinal uses because different parts of the tree are reported to possess various pharmacological activities ranging from its leaves, seeds, oil, sap, bark, roots to its flowers, are all widely used in traditional and alternative medicine. The leaves especially, are highly nutritious, rich in protein iron, calcium, potassium, phosphorus, vitamin A, C and D, riboflavin, nicotinic acid, folic acid, pyridoxine, essential amino acids, fatty acids and antioxidants such as vitamin C, β-carotene, flavonoid and phenolics (Stohs and Hartman, 2015). The therapeutic potential of MO varied, ranging from its antidiabetic, antihypertensive, antimicrobial, antineoplastic, antihyperlipidemic, antipyretic, antiulcer, anti-inflammatory, diuretic, cardioprotectant, hepatoprotectant and antioxidant properties (Stohs and Hartman, 2015). The MO leaves possess nootropic (cognitive enhancer) activity by providing protection in hypobaric hypoxia via altering the brain monoamines which are associated with memory loss (Ganguly and Guha, 2008).

The nervous system is known to be rich in both unsaturated fats and iron. Despite the presence of many defence mechanisms, the nervous system has a poor capacity in coping with oxidative stress and demonstrates limited regenerative capacity (Barnham *et al*., 2004). The brain and the rest of the nervous system have high metabolic activity that requires high metal ion concentrations for maintaining many of its functions (Igado and Olopade, 2016), which makes it particularly vulnerable to oxidative stress and damage (Ganguly *et al*., 2005). Many studies have shown evidence that oxidative stress is a causative and contributing factor in the pathogenesis of neurodegenerative diseases. Neurodegenerative diseases are a group of neurological disorders with diverse clinical importance and aetiologies, characterized by the progressive loss of specific neuronal cells, mostly in areas of cognitive functions such as the cerebral cortex and hippocampus (Barnham *et al*., 2004; Ganguly *et al*., 2005). These are commonly the case in neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease and amyotrophic

lateral sclerosis and other related neurological conditions (Barnham *et al*., 2004). MO has been proven to be rich in antioxidants especially in its leaves and seeds and this has increased interest in its use as a therapeutic agent for related pathologies. Ganguly *et al*., (2005) demonstrated that treatment with 250 mg/kg b.w of MO for 14 days improved memory through its antioxidant properties evident from the increased superoxide dismutase level, increased catalase activity and decreased lipid peroxidation activity in the cerebral cortex of a colchicine -infused Alzheimer rat model.

Also, Ganguly and Guha (2008) studied the effect of chronic (14 days) oral administration of various doses of ethanolic extract of MO leaves on the brains of rats affected by Alzheimer's disease. It was observed that there was a dose-dependent improvement in neurocognitive performance with MO leaves extract, with the effect being lowest at 50-100mg/kg and maximal at 250 mg/kg. The MO leaves extract improved memory by increasing the correct choices in daily trials and decreasing the latency time. The extract also significantly increased the levels of monoamines and also improved electrical activity in distinct areas of the brain in rat model of Alzheimer's disease.

Sutalangka *et al*., (2013) demonstrated the effectiveness of the oral administration of the aqueous extract of MO leaf as a potential cognitive enhancer and neuroprotectant in rats having cholinotoxin-induced dementia. Doses of 100 – 400 mg/kg of the extract were given for 7 days, which improved spatial memory, shown by the significant reduction in the escape latency, and increased retention time when subjected to Morris Water maze. The extract showed a decrease in malondialdehyde levels and increased levels of superoxide dismutase and catalase. There was also decreased neurodegeneration in the cornu ammonis (CA1, CA2, CA3) and dentate gyrus of the hippocampus. These findings corresponded with that of Roy (2014) who observed that the ethanol leaf extract of MO reversed cognitive deficits in colchicine-induced Alzheimer's disease in rats, and also attenuated other cholinotoxic effects such as, induction of frontal, cortical and hippocampal concentrations of acetylcholine (Ach) and choline acetyl transferase (ChAt) activity. Other markers for oxidative stress were also positively affected.

There are some derivatives of MO such as glucosinolates that have been reported to be effective against neurodegenerative conditions. Glucosinolates and their breakdown products like isothiocyanates have been reported to be present in Moringaceae plants and as such, have attracted research interest, because of the neuro protective potentials (Giacoppo *et al*., 2015). Some studies have also reported that R, S-Sulforaphane–SFN (a type of glucosinolates), offers protection from primary cortical neuronal injuries caused by dopamine (an oxidized products). It also protects mesencephalic dopaminergic neurons from cytotoxicity and oxidative stress by preventing ROS production through the removal of intracellular quinone products and DNA fragmentation (Vauzour *et al*., 2007; Igado and Olopade, 2016).

MO was observed in various studies to be protective against brain dysfunction and damage caused by cerebral ischemic injury. Kirisattayakul *et al*., (2013) reported the potential benefit of the hydroalcohol MO extract administered at oral doses of 100-400 mg/kg for 2 and 3 weeks respectively, in decreasing brain infarct volume, and also preventing focal cerebral ischemia. This effect was considered to be due to decreased oxidative stress demonstrated in the hippocampus, cerebral cortex and the striatum. A study by Zhou *et al*., (2018) investigated the neuropharmacological properties of 70% ethanolic MO seed extract (MSE) on cognitive impairment induced by the administration of scopolamine. Results showed that MSE ameliorated learning and memory impairment and also enhanced cholinergic system reactivity and neurogenesis in the hippocampus, via activation of the Akt, ERK1/2, and CREB signalling pathways. MSE was also found to have a dose-dependent preventive effect on ischemic cerebral injury with the optimal dose at 500 mg/kg and a therapeutic effect on acute cerebral ischemic injury within 4 hr after reperfusion therapeutic window (Zeng *et al*., 2019). Zeng's study of 2019, showed that treatment with MSE alleviated spatial cognitive deficits, promoted hippocampal neurogenesis, neuroplasticity, and cholinergic neurotransmission system and also enhanced animal survival, during the recovery period of both acute and chronic stages of ischemic stroke. However, MSE treatments had no effect on the generation of glial cell.

MO leaves and seeds were reported to have ameliorative effects against metal toxicity (Velaga *et al*., 2014). The integrity of brain regions such as the cerebellum, hippocampus, frontal cortex and brain stem were observed in a study to have been restored following Moringa treatment (500 mg/kg) after lead exposure (Velega *et al*., 2014). This agrees with a study done by Owolabi *et al*., (2014) in which results showed that MO produced ameliorative effects against lead toxicity in the cerebral cortex. Another study by Ekong *et al*., (2017), investigated the neuroprotective effect of MO ethanolic leaf extract on aluminum-induced temporal cortical degeneration in rats, and found that MO has a protective effect against aluminum neurotoxicity. Their study revealed that the temporal cortex section of the AlCl3+MO group showed little to no adverse histomorphology compared to the aluminum chloride group. Nissl substance was found in most of the temporal cortical neurons as compared to the aluminum chloride group.

The neuroprotective effect of MO was revealed by restoration of neurohormones (GHRH, SRIH levels), antioxidant enzymes (peroxide, cholinesterase activities and glutathione (GSH) levels), lipid MDA content, and protein carbonyls (PC) oxidation following intra uterine rat exposure to nicotine, which is neurotoxic. It was neuroprotective to both the mother and the offspring (Abdu, 2013). Omotoso *et al*., (2018) studied the effect of MO on nicotine-induced cerebellar damage in terms of histomorphological and neurobehavioural changes and observed that there were cytoarchitectural distortions, degenerated Purkinje cells, severe chromatolysis of neuronal cells of the cerebellar cortical layers, reduced locomotor activities and increased anxiety in the nicotine treated groups which were absent in the MO treated groups. They also observed that MO can mitigate the nicotine-induced reduction in cerebellar weight, with possible ameliorative effects.

It is important to use in vitro cellular models because it forms an indispensable aspect of understanding cellular and molecular processes in specific tissue, organ or disease pathogenesis (Igado *et al*., 2018). The pathogenesis of many neurodegenerative and neurological disorders presents with cognitive, learning and memory dysfunctions resulting from damage or injury to different parts such as cerebral cortex, hippocampus, amygdala and thalamus (Barnham *et al*., 2004; Ganguly *et al*., 2005).

Some studies have demonstrated evidence of neurotropic and neurodegenerative disorders in neural cell cultures and animal models. Hannan *et al*., (2014) conducted a study to evaluate the neurotropic and neuroprotective potentials of MO leaf on primary hippocampal neurons. The results showed that with an optimal concentration of 30 µg/mL of MOE, there was dose-dependent promotion of neurite outgrowth with an increased neuronal viability by protecting neurons from naturally occurring cellular injury or death. Also, significant promotion in neuronal differentiation rate modulated dendritic complexity and axonal development facilitated synaptogenesis. β carotene which is one of the major compounds of MOE, was observed to promote neurite outgrowth although the increase was not comparable with the effect of MOE but it could be said to be responsible for the multiple branching and differentiations observed because β-carotene can induce cell differentiation in neurons (Lee *et al*., 2013).

There are lots of extensive literatures on the use of MO in treating various conditions such as diabetes, liver pathologies, hyperlipidemia, hypertension, hypoglycaemia and many related conditions both in in vivo and in vitro studies but there is need for more research on the use of MO and its derivatives to treat neurodegenerative, neurological or nervous system related conditions. There is also very little data on in vitro effect of MO on the brain and nervous system in general. Igado *et al*. (2018, 2020) reported the isolation of a pure compound from MO leaves and its effectiveness both in vitro and in vivo in treating neurodegeneration. In Nigeria, the use of alternative medicine is increasing and natural herbal solutions are being used to treat various ailments. Hence, the need for neuroscientists to perform further research on the utility of MO in the prevention, and treatment of neurological diseases.

***Nigella sativa*:** *Nigella sativa* (NS) is an annual flowering plant of the family *Ranunculaceae*, widely cultivated in different parts of the world such as the Eastern Mediterranean, Northern Africa, West Asia and Indian Subcontinent (Beheshti *et al*., 2016). It has beautiful, delicate, pale blue and white flowers and its leaves are green and finely divided. The inflated capsule of its ripe fruit is comprised of 3-7 united follicles, each containing numerous oval shaped black tiny seeds (Randhawa and Alenazi, 2016). NS is a widely used natural remedy as its seeds and herbs have been well known to promote health and fight diseases such as asthma, diabetes, hypertension, kidney and liver dysfunctions, common cold, rheumatic diseases, cancer, obesity, and cardiac diseases. It has also been used as anti-inflammatory, anti-anxiety, antipyretic, anti-diarrhoea, and protects against fatigue and memory impairments for centuries, especially in the Middle East and South East Asia (Beheshti *et al*., 2016; Randhawa and Alenazi, 2016; Asiaei *et al*., 2017). The NS seeds are also known as Black Seed or Black Cumin in English, and in different other languages as Habba Al-Sauda or Habba Al-Barakah in Arabic, Kalonji in Urdu, Siyah Daneh/Shonaiz in Persian, Kalajira' in Bengali, Mangrail in Hindi/Nepali and Corek Out in Turkish language (Beheshti *et al*., 2016; Randhawa and Alenazi, 2016; Yimer *et al*., 2019). The black seeds are rich in proteins, fat, carbohydrates, fiber, amino acids, volatile and fatty oils, vitamins (A, B1, B2, B3 and C), minerals (Calcium, Potassium, Copper, Iron, Zinc), flavonoids and many other active components such as thymoquinone, dithymoquinone, thymohydroquinone, thymol, carvacrol, nigellicine, nigellimine-N-oxide, and alpha-hederin (Randhawa and Alenazi, 2016; Yimer *et al*., 2019). NS has been shown to have beneficial effects on the nervous system through its antioxidant properties. Thymoquinone (TQ), a major active component of NS seeds and oil (Beheshti *et al*., 2016) has been shown to inhibit non-enzymatic lipid peroxidation in liposomes and also possess cytoprotective and antioxidant effects (Asiaei *et al*., 2017; Fanoudi *et al*., 2019). TQ has enhancing effects on learning and memory, as well as protection against the development of neurodegenerative disease and other conditions such as anxiety/depression, epilepsy, ischemic stroke, brain inflammatory diseases and cancer (Farkhondeh *et al*., 2018; Fanoudi *et al*., 2019). Studies by Beheshti *et al*., (2016) demonstrated that NS inhibited AChE activities thus enhancing ACh transmission, and its effects in the encoding of new memories in the hippocampus. In the experiment, AChE levels/activities were compared in four group of Wistar rats: normal saline for two weeks (as control); NS extract (200 and 400 mg/kg/day, i.p.) respectively for two weeks and then Sco after. The result showed that AChE levels in the cortex was highest in Sco group (0.072±0.008 µmol/g tissue/min), followed by the Sco+NS 200 mg group (0.048±0.003 µmol/g tissue/min), then the Sco+NS 400 group (0.031±0.004 µmol/g tissue/min), and finally the control group (0.024±0.002 µmol/g tissue/min). The significantly lower levels of AChE in the Sco+NS extract groups compared to the scopolamine groups demonstrated the ability of NS extract to inhibit or reverse scopolamine induced AChE activities in the cortex (Hosseini *et al*., 2014).

In 2019, Fanuodi *et al*., studied the effect of hydroalcoholic extract of NS (NSE) and its constituent TQ on AChE activity, with cerebral hypoperfusion induced by permanent occlusion of both common carotid arteries in rats (2VO). The study revealed that AChE activity was significantly increased in the hippocampus of hypoperfused rats compared to the control group; and that, administration of increasing doses of NS from 200 mg/kg to 400 mg/kg reduced the levels from 0.62 ± 0.02 µmol/min/mg protein to 0.45 ± 0.05 µmol/min/mg protein respectively. Treatment of the cerebral hypoperfused animals with TQ 20 mg/kg showed a dose dependant decrease in AChE activity (Fanuodi *et al*., 2019). In addition, Imam *et al*. (2018a) studied the effect of NS oil (NSO) ion the amygdala of rats induced with Chlorpyrifos (CPF). They noticed that NSO prevented the overproduction of reactive oxygen species (ROS) and nitric oxide (NO) and markedly reactivated Acetylcholinesterase (AChE) activities in the rats' amygdala. The NSO treatment preserved neurogenic cells in the amygdala and subsequently improved amygdala-dependent behaviours in the treated rats. They concluded that the antioxidant efficacy of NSO could be efficacious in CPF induced neuro-cognitive toxicity in rats. Dichlorvos (DDVP)-induced inhibition of AChE activities in the different brain regions. The authors demonstrated that acute and chronic exposure to oral DDVP (8.8 mg/kg) inhibited AChE activities in varying degrees in the following brain regions when compared to the control: cerebellar cortices (86.1%), hippocampus (40.6%), frontal cortices (33.2%), medulla (21.5%), spinal cord (14.8%) and occipital cortices (8.9%) respectively.

The passive avoidance (PA) task is also an experiment that is based on fear-aggravated test for the evaluation of learning and memory in rodents. During the test, rodents learn to avoid an environment in which an aversive stimulus (such as a foot-

shock) has been previously delivered (Beheshti *et al*., 2016). Furthermore, Azzubaidi *et al*., (2012) assessed the effect of NSO treatment on preservation of spatial reference, long-term memory (LTM), short-term (STM) and spatial working memory (SWM) of cerebrally hypo-perfused rats induced by 2VO surgery. Their result showed that NSO-treated rats demonstrated significantly shorter mean escape latency time and longer time spent in target zone in the morris water maze (MWM) test compared to that of the 2VO untreated group, suggesting that NSO attenuated the 2VO-induced learning and memory impairment and demonstrated strong capacity to preserve retrieval of remote spatial reference memory. In 2015, Seghatoleslam *et al*., observed that rats given 200mg/kg and 400 mg/kg, i.p. of NSO before penthylenetetrazole (PTZ) injection performed better in passive avoidance (the PA) test than the PTZ only group suggesting that NSO was capable of improving learning and memory impairments caused by PTZ-induced repeated seizure in rats. The experiment was replicated by Vafaee and colleagues with 400 mg/kg, i.p, NSE with similar results (i.e. improved performance of the NSE-treated rats on PA and MWM tests in comparison to the PTZ group (Vafaee *et al*., 2015). Beheshti *et al*. used MWM and PA tests to show that treatment with 100 - 400 mg/kg of *Nigella sativa* extract (NSE) ameliorated the deleterious effects of hypothyroidism on learning and memory during neonatal and juvenile growth. The feeding of lactating rats with NSE during neonatal and juvenile growth periods also showed an increase in their learning and memory performance (Beheshti *et al*., 2016). Hosseini *et al*., (2015) also investigated the effect of NSE on memory impairment of scopolamine Sco-induced rats, by pre-treating with NSE (200 and/or 400 mg/kg, i.p.) for two weeks. Their results revealed that the NSE treated animals had better execution in the MWM and PA tests than as the control group, suggesting that NSE had beneficial effect on spatial memory impairment, by reversing memory deficit in the rats. This was supported by a later by a study that demonstrated that NSO treatment significantly improved the long-term memory (LTM), short-term (STM) and reference memory trials, and reversed Chlopyrifos (CPF)-induced learning and memory impairment by increasing relative memory consolidation in rats (Imam *et al*., 2018b). The reversal effect of NSO on Dichlorvos (DDVP)-induced cognitive decline in the hippocampus was also studied by Imam *et al*., (2018c), and the result showed that NSO treatment significantly enhanced escape latencies in both LTM and STM trials. The effect of NSE and its active constituent thymoquinone (TQ) on learning and memory impairment following cerebral hypoperfusion after permanently bilaterally occluding the common carotid arteries in rats was studied by Fanoudi and colleagues. They observed that they discovered that NSE (400mg/kg/day) and TQ (40mg/kg/day) significantly improved learning performances in a dose-dependent manner by significantly decreasing the mean latency time when subjected to the MWM test. The experiment thus suggests that NSE or TQ could ameliorate chronic hypoperfusion-induced cognitive impairments demonstrated by the improved working memory of treatment groups on the MWM test (Fanoudi *et al*., 2019). Oxidative stress is fundamental in neurological and neurodegenerative disorders due to high oxygen consumption and lipid rich content of the brain (Fanoudi *et al*., 2019). It results from an imbalance in pro-oxidant/antioxidant homeostasis, which leads to the generation of toxic reactive oxygen species (ROS). Antioxidants are molecules that inactivate them by reacting preferentially with ROS. Different studies have shown that NSE has antioxidant properties (Barnham *et al*., 2004; Beheshti *et al*., 2016; Randhawa and Alenazi, 2016). Hosseinzadeh *et al*., (2007) reported that NSO and TQ protect the brain through their antioxidant activities by preventing lipid peroxidation in hippocampus of global cerebral ischemia-reperfusion injured rat models. Akhar *et al*., (2012) also demonstrated that pre-treatment with NSE in global cerebral ischemia-reperfusion injured rat models significantly increased levels of glutathione (GSH), superoxide dismutase (SOD) and catalase (CAT) while simultaneously reducing the infarct volume significantly when compared to the untreated middle cerebral artery occlusion (MCAO) group. The NSE significantly reduced the thiobarbituric acid reactive substance (TBARS) when compared with the MCAO group in the same study (Akhar *et al*., 2012).

The reduction in infarct volume and TBARS as well as the increase in levels of GSH, SOD and CAT shows that NSE has neuroprotective, antioxidant and free radical scavenging properties. Another study by Fanuodi *et al*., (2019) noticed the on the antioxidant effect of NSE and its constituent TQ in 2VO–induced cerebral hypo-perfused rats with, observed that the NSE-treated rats had significantly higher SOD levels and lower malondialdehyde (MDA) level than untreated rats. In a study by Sandhu and Rana (2013), NSE administered at a dose of 200- mg/kg – 400 mg/kg, i.p caused significant reversal in chlorpromazine (CPZ)-induced catalepsy by reducing cataleptic scores, reducing MDA and nitric oxide (NO) levels and increasing the total antioxidant capacity (TAC), GSH and total protein levels suggesting that NSE has antioxidant properties, and therefore can possess therapeutic effect against Parkinson disease in CPZ-induced animal PD models. Hosseini *et al*., (2015) observed that a 2-week treatment with 200- mg/kg – 400 mg/kg NSE in Scopolamine- induced memory impaired rat model, significantly decreased the lipid peroxidation caused by free radical mediation, indicated by the decrease in MDA level and an increase in total thiol concentration, thus suggesting that treatment with NSE reversed Scopolamine -induced oxidative stress on brain tissue. In addition, Vafaee *et al*., (2015) also showed that NSE pretreatment attenuated the PTZ-induced repeated seizures and oxidative damage to the brain by decreasing MDA level and increasing total thiol concentration. Abbasnezhad *et al*., (2015) investigated the effect of NSE seeds on oxidative stress in the hippocampus of a streptozotocin (STZ)-induced diabetic rat model, and observed that at the dose of 200 mg/kg, NSE significantly decreased MDA levels and increased thiol content in hippocampus compared to the untreated group.

A study by Beheshti *et al*., (2017) in which lactating rats were fed with dietary supplementation of 400 mg/kg NSE during neonatal and juvenile growth periods, observed reduced MDA level and increased total thiol concentration in the hippocampus but reduced MDA level and normal thiol content in cortical tissues suggesting that feeding very young and growing rats with NS increased TAC and reduced oxidative stress in the brain tissue. The antioxidant effect of NS on the cortical and hippocampal tissues was also observed in hypothyroid rats in a study by Beheshti *et al*., (2017), suggesting that NS can protect brain tissues against oxidative stress and damage in hypothyroidism. In a study investigating the mitigating effects of NSO on DDVP-induced hippocampal damage in Wistar rats, Iman *et al*., (2018c) observed that post-

treatment with NSO reversed the DDVP induced NO and ROS outburst in the hippocampus. NSO was also found to significantly reverse Chlopyrifos (CPF)-induced oxidative and neurogenic damages in rats by reducing ROS generation and NO levels (Imam *et al*., 2018b). Neuronal integrity is very essential for the circuitry connectivity and network. It forms the basis of brain connectivity. Some activities that could hamper the integrity of the neurons are degeneration of synapses and their cellular components and microglia depletion. Kanter (2008b) investigated the possible effect of NS and TQ on neurodegeneration in rats' hippocampus after chronic toluene exposure (3000 ppm, 8hr/day, 6 days/week) in rats, and observed that the intensity of neuronal changes, severity of degenerative changes in the cytoplasm and nuclei of the cells were less in the NS and TQ treated groups than the toluene treated groups. The result also showed that the immune-reactivity of degenerating neurons were markedly reduced and the dark stained nucleus and distorted nerve cells were absent in the TQ and NS treated groups. Previously, Kanter (2008a) had evaluated the possible protective effects of NS and TQ on neuronal injury in the frontal cortex and brain stem after chronic toluene exposure in rats and observed that NS and TQ treatment had a mitigating effect on the neuronal ultrastructure of all the brain tissues examined. In some in vitro studies, NSO pretreatment of cerebellar neurons cell culture before beta-amyloid protein intoxication improved significantly neuronal cell viability as compared to untreated cerebellar neurons cell culture (Ismail *et al*., 2008).

The neuroprotective effect of NSE after pentylenetetrazole (PTZ) -induced seizures in rats showed that NS at effective dose of 400 mg/kg prevented neural damage by preventing the production of dark neurons in regions of the hippocampus due to PTZ induced seizures (Seghatoleslam *et al*., 2015). The neuroprotective effect of TQ (10 mg/kg) was also investigated in 6-hydroxydopamine (6-OHDA) rat model of early hemi-parkinsonism, and the result showed that TQ attenuated loss of substantial nigra pars compacta (SNC) neurons and the selective loss of SNC dopaminergic neurons which are direct cause of neurodegeneration in patients with Parkinson disease (PD). Sedaghat and colleagues disclosed that TQ also significantly decreased apomorphine-induced rotations which are considered as reliable indications of nigrostriatal dopamine depletion. The preservation of nigrostriatal neurons (SNC) and reduction in midbrain levels of MDA in the presence of TQ suggests that TQ protects against SNC neurodegeneration induced by neurotoxin 6-hydroxyldopamine (6-OHDA) (Sedaghat *et al*., 2014).

The neuroprotective effects of NS in the hippocampal neurons of rats exposed to global ischemia-reperfusion cerebral hypoperfusion model have been investigated at different times by many researchers (Akhar *et al*., 2012; Azzubaidi *et al*., 2012). The results showed that NS had inhibitory effects against neuronal oedema in supportive neuronal tissue on the hippocampus in a dose-dependent manner, suggesting possible neuroprotective effects on the cerebral and hippocampal neurons induced by ischemia and exacerbated by intracellular oxidative stress and neuro-inflammation (Azzubaidi *et al*., 2012). In 2017, Asiaei and co-researchers performed a stereological study on the effect of NS plant extract in propylthiouracil (PTU)-induced hypo-thyroid rats on neuronal damage and hippocampal volume during neonatal and juvenile growth. NS extract at in various doses (0.05%, 0.1% and 0.2%) were given with PTU simultaneously in drinking water at gestation day 0 for the pregnant rats and continuously for the pups during lactation and infancy period for 60 days (Asiaei *et al*., 2017). The result showed that NS treatments in tested doses significantly attenuated the neuronal damage caused by PTU by reducing the number of apoptotic cells, mean number of dark neurons per unit area in all regions of the hippocampus, and preventing the production of dark neurons. Imam *et al*., (2018c), evaluated the neuroprotective efficacy of NSO against DDVP-induced hippocampal neurotoxicity and found that NSO reversed the loss in density of Ki67+ cells (proliferating cells) in the hippocampal subfields and subventricular zone (SVZ) observed in the dichlorvos (DDVP) treated group. This was corroborated in another study that investigated the efficacy of NSO in ameliorating chlorpyrifos (CPF) induced neurogenic damages with subsequent effects on learning and memory function in rats. NSO prevented loss in density and denaturation in the Ki67+ cells in the hippocampal subfields, dentate gyrus (DG) and subventricular zone, caused by the CPF insult, which suggests that NSO is a potent anti-inflammatory agent capable of improving cell proliferation in the DG and consequently, the integration of the adult born new cells into the learning and memory circuitry (Imam *et al*., 2018b).

CONCLUSION

African medicinal plants are gaining more recognition as they play vital roles in the continent's healthcare system. The medicinal plants and their active components have been shown from the results of the several studies in this review to improve cognitive dysfunction, learning and memory performance, neurodegeneration and neurotoxicity. This review article summarized reports of in vitro and in vivo studies of *Telfairia occidentalis*, *Garcinia Kola*, *Ocimum gratissimum*, *Moringa oleifera*, *Nigella sativa* on different parts of the brain as they affect cognitive performance and ameliorate neuronal pathologies.

A lot of challenges need to be addressed, so that their full potential to viable and effective treatment of neurological conditions can be recognized. We therefore challenge African neuroscientists to put in more efforts for the effective use of these plants in their research. More collaboration is also being advocated with pharmaceutical companies, policy makers as well as the government to realize the goal of "gown to town", and preventing the research from just staying on the shelves. Future studies are required to evaluate the effects of these plants on other neurological conditions such as hydrocephalus, spinal bifida and brain tumours which we have observed seems to be currently lacking in literature, as of the time of this report.

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