Review
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Methyl Jasmonate: Behavioral and Molecular Implications in Neurological Disorders

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Methyl jasmonate (MJ) is a derivative of the jasmonate family which is found in most tropical regions of the world and present in many fruits and vegetables such as grapevines, tomato, rice, and sugarcane. MJ is a cyclopentanone phytohormone that plays a vital role in defense against stress and pathogens in plants. This has led to its isolation from plants for studies in animals. Many of these studies have been carried out to evaluate its therapeutic effects on behavioral and neurochemical functions. It has however been proposed to have beneficial potential over a wide range of neurological disorders. Hence, this review aims to provide an overview of the neuroprotective properties of MJ and its probable mechanisms of ameliorating neurological disorders. The information used for this review was sourced from research articles and scientific databases using 'methyl jasmonate', 'behavior', 'neuroprotection', 'neurodegenerative diseases', and 'mechanisms' as search words. The review highlights its influences on behavioral patterns of anxiety, aggression, depression, memory, psychotic, and stress. The molecular mechanisms such as modulation of the antioxidant defense, inflammatory biomarkers, neurotransmitter regulation, and neuronal regeneration, underlying its actions in managing neurodegenerative diseases like Alzheimer's and Parkinson's diseases are also discussed. This review, therefore, provides a detailed evaluation of methyl jasmonate as a potential neuroprotective compound with the ability to modify behavioral and molecular biomarkers underlying neurological disorders. Hence, MJ could be modeled as a guided treatment for the management of brain diseases.

KEY WORDS: Methyl jasmonate; Neuroprotection; Behavior; Neurodegenerative diseases; Depression; Anxiety.

INTRODUCTION

Jasmonates are cyclopentanone phytohormones that play an imperative role in the defense of plants against abiotic stressors and pathogenic invasions [1]. Although they were initially isolated from *Jasminum grandiflorum* L., a plant mostly found in tropical regions [2], they are extensively distributed in plants and some microorganisms [1]. They are cell regulators, known to activate intracellular signaling mechanisms in plant growth, defense, and response to stress triggers [3]. Their biosynthesis from linolenic acid in plants is analogous to the synthesis of eicosanoids from arachidonic acid in animals [3,4]. The family of jasmonates includes Cis-jasmone (CJ), Jasmonic acid (JA), and Methyl jasmonate (MJ) [3]. Of all the members of the Jasmonates family, MJ is the most studied. MJ is an adaptogenic phytohormone [5] released by plant cells in response to environmental stress, injury, and pathogen invasions. It induces the synthesis of proteinase inhibitor proteins, which are involved in plants' defense against a variety of biotic and abiotic stressors [5]. On exposure of plants to stressors, MJ is synthesized, resulting in the activation of the proteinase inhibitor gene and subsequently, the expression of proteinase inhibitor proteins [5,6]. Its involvement in the adaptation of plants to stress is further supported by its increased level following plants' exposure to stressors [5,7]. It also plays a vital role in intracellular signaling and defense in response to pathogenic

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invasions [1]. One of the numerous adaptogenic properties of MJ relies on its ability to regulate the activities of antioxidants and combat the harmful effects of oxidant molecules [8].

Jasmonates and its derivatives are widely recognized in the practice of aromatherapy for depression, tension, nervousness, anxiety, and mental alertness [5,9]. Earlier experimental studies on MJ were largely on its therapeutic potentials on cancer cells that have attracted global recognition as a promising antitumor agent. The uniqueness of MJ in cancer pathology is related to its ability to preferentially kills cancer cells via several unrelated molecular mechanisms without causing damage to normal body cells. These findings have been described as inspiring evidence that may encourage its development for the treatment of cancer and other debilitating diseases that require prolonged therapy [1,5,7,10-15]. Meanwhile, the possibility of its potential usefulness in neuropsychiatric disorders stemmed from the reports of Hossain *et al.* [16], which have shown that MJ exhibited sedative effect and enhanced GABAergic neurotransmission. These findings have led to extensive studies on the effects of MJ on neurological disorders and the mechanisms underlying its neuroprotective activity in rodents [17-23]. This review presents the documented evidence on the neuroprotective activities of MJ and the mechanisms underlying its therapeutic potentials in neurological disorders. It also highlights the mechanisms by which the adaptogenic-like property of MJ could help alleviate chronic stress-induced psychopathologies.

SAFETY AND TOXICITY

The ability of MJ to offer cellular protection has generated more attention for its potential use as a therapeutic agent in various disorders and diseases. This has led to the screening of MJ for potential toxicity by several authors [1,2,7,10,12,24,25]. In an investigation by Flescher [12], and Cohen and Flescher [1], MJ administration preferentially killed cancer cells, without affecting normal body cells. Umukoro and Olugbemide [2] also reported no case of toxicity or death in mice after administering 100－500 mg/kg of MJ. However, results of several studies on acute toxicity, skin irritation, mucous membrane (eye) irritation, skin sensitization, phototoxicity, and photoallergy of MJ indicated that the LD_{50} for oral administration was $>$ 5 g/kg, and for skin use, the LD_{50} was $>$ 2 g/kg. Additionally, no irritation was observed in the human repeated-insult patch test and several animal studies. Furthermore, no irritation was detected in the mucous membrane test. Sensitization reactions in animal and human studies and photo-irritation and photoallergy studies in humans did not show any significant toxicity [25]. This finding further support previous investigations, which show that MJ is safe, as it is not toxic to normal body cells [1,7]. Likewise, the US Federal Environmental Protection Agency in 2013 issued MJ an exclusion for tolerance requirement test as it was observed to be naturally-available in human nutrition [26]. The Food and Agriculture Organization/World Health Organization also approved MJ amongst other food additives [27]. MJ was also detected to have no toxic outcome in all experiments involving all drug routes [14,25].

METHYL JASMONATE MODIFIES BEHAVIORS ASSOCIATED WITH NEUROLOGICAL DISORDERS

MJ has been implicated in various behavioral modifications, such as anxiety, depression, aggression, memory among others, using experimental animal models. These are summarized in Figure 1 and Table 1.

Anxiety/Anxiolytic Activity

Anxiety is a disorder of the central nervous system (CNS) associated with an imbalance between excitatory and inhibitory impulses in the brain. These imbalance areas result in decreased GABAergic and increased glutaminergic neurochemical pathways respectively [28-32]. Anxiety manifests in various ways like fear, eating disorder, worry, suicidal tendencies in humans [22]. Several studies have explored the anti-anxiolytic potential of MJ. Most of which used mice models. Umukoro *et al.* [22] demonstrated the anti-anxiolytic effect of MJ on unpredictable chronic mild stress (UCMS)-induced mice while studying the explorative behavior of the mice in a light/dark transition test and elevated plus maze (EPM) test. In the EPM test, MJ reduced the frequency and extent of time spent in the closed arm in UCMS-induced mice. MJ also reduced the time spent by mice in the dark compartment in a light/dark transition test of UCMS-induced mice. All these observations suggest the anti-anxiogenic activity of MJ [22].

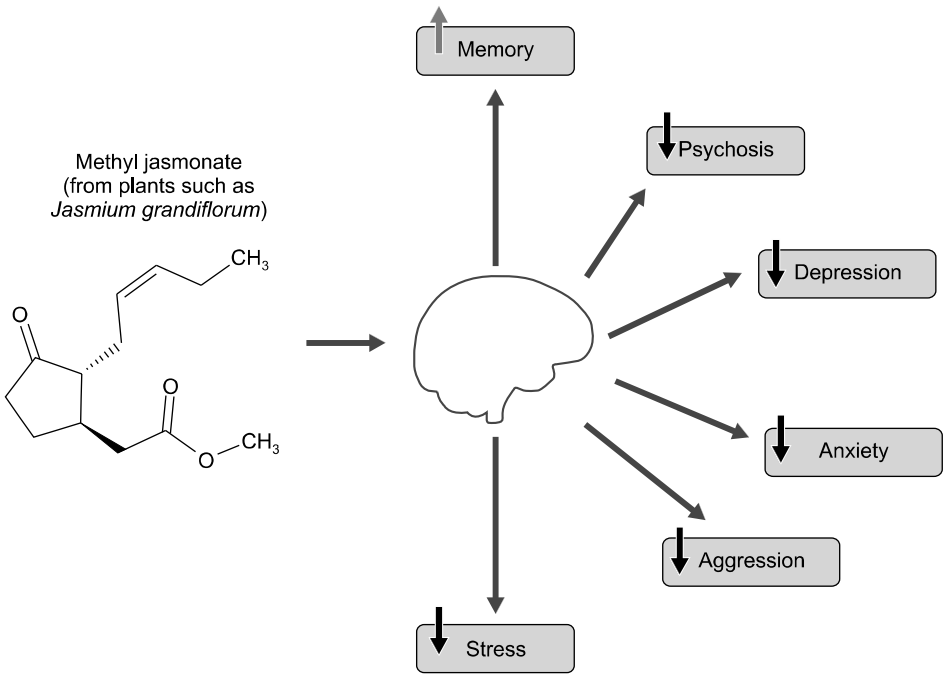

Fig. 1. MJ improves behavioral deficits associated with neurological disorders.
MJ, Methyl jasmonate.

Table 1. Summary of behavioral modifications of MJ in animal models

Disorders	Models	Effects	References
Anxiety	Elevated plus maze (EPM)	Reduced frequency and duration of time spent by UCMS-induced mice in the closed arm	[21]
	Light/dark test	Reduced time spent in the dark compartment	[21]
Depression	Tail suspension test	Reduced latency period in UCMS-induced mice	[17,36]
	Forced swim test	Reduced immobility period	[36]
	Sucrose preference test	Increased sucrose intake initially reduced by UCMS	[17]
Aggression	Isolation-evoked paradigm	Decreased aggressive behaviors	[41]
	Resident-intruder paradigm	Decreased aggressive behaviors	[41]
Memory	Passive avoidance paradigm	Increased latency period	[18]
	Y-maze	Increased alternation behavior	[19,20]
	Object recognition test	Increased discrimination index	[19]
Antipsychotic	Bromocriptine-induced stereotype	Reduced stereotyped behavior	[16]
	Ketamine-induced stereotypy	Reduced stereotyped behavior	[16]
Anti-stress	Forced swim endurance test	Delayed first occurrence of immobility shortened immobility period increased active swimming time	[22]
	Anoxic tolerance test	Prolonged latency to the first appearance of anoxic convulsions	[22]
	Unpredictable chronic mild stress	Reduced stress-induced memory impairments Reduced stress-induced anxiety behaviors	[21]

MJ, Methyl jasmonate; UCMS, unpredictable chronic mild stress.

Depression

Depression is a prevalent disorder that negatively impacts the quality of life worldwide. It affects about 20% of the world's population and is typically higher in females than in males with a ratio of 5:2. Preclinical and clinical investigations have implicated serotonin and norepinephrine in its pathogenesis [33,34]. The deficiency of these monoaminergic transmitters in the brain is reported to be one of the most significant etiological factors for the cause of depression. The recurrent nature of depression and its numerous triggers have made it difficult to manage [34-36]. These have led to increased interest in researching more effective antidepressants [37,38]. In a study conducted by Adebesin *et al.* [18], and acute stress model of

tail suspension test (TST) was adapted to investigate the antidepressant-like property of MJ in UCMS-induced mice. An increased latency period was observed in UCMS-induced mice. This period was significantly reduced, following treatment with MJ, indicating antidepressant-like property [18]. This finding is consistent with that of Umukoro *et al.* [37] where acute stress models of TST and forced swim test (FST) were adapted in mice to study the antidepressant activity of MJ. MJ significantly decreased the period of immobility in both tests. Adebesin *et al.* [18] went further by using the sucrose preference test to evaluate the anti-depressant activity of MJ. This test is used to evaluate anhedonia (inability to experience pleasure), a key symptom of depression in humans. They reported that MJ attenuated impaired sucrose intake in rodents initially exposed to UCMS [18]. Biochemical evaluations have also been carried out to confirm the anti-depressant property of MJ. In a study by Zomkowski *et al.* [39], MJ reduced serotonin levels [39]. Studies have shown also that the anti-immobility exhibited by antidepressants in the FST and TST is mediated through the facilitation of both serotonergic and noradrenergic neurotransmissions [37]. Additionally, Umukoro *et al.* [37] employed the yohimbine lethality test to elucidate the role of monoaminergic transmitters in the antidepressant-like activity of MJ. Antidepressants are known to synergistically potentiate the lethality of yohimbine. In the study, intraperitoneal injections of MJ at doses of 25 mg/kg and 50 mg/kg, significantly increased the lethal effect of yohimbine. Yohimbine is an α_2-adrenergic receptors antagonist that stimulates sympathetic centers in the brain, resulting in increased sympathetic discharge in the CNS and peripheral nervous system (PNS) [37]. Antagonism of α_2-adrenergic receptors promotes the release of noradrenaline due to increased central sympathetic activity and induces serotonin release, further contributing to the overall toxicity caused by yohimbine. MJ synergistically potentiate the lethality of yohimbine by allowing more amines to get to receptors in high quantities, either by impeding their reuptake or by decreasing their inactivation, thus suggesting the involvement of monoaminergic transmitters in its antidepressant property in mice [37].

Aggression

Aggression is a deliberate series of actions that inflict harm on another organism and is a major component of the stress-syndrome. It is characterized by low tolerance to frustration and studies have shown that feeling of frustration results from prolonged stress [40,41]. Aggression may manifest itself as a defensive or offensive behavior. Although aggression and depression are diagnostically categorized differently by the psychiatric classification systems Diagnostic and Statistical Manual of Mental Disorders 4th edition, they are however clinically and biochemically related [35,37]. The serotonergic system is implicated in both disorders [35]. This is proven by alleviated symptoms of depression and aggression when serotonin receptor agonists and uptake inhibitors were administered [35]. In a study by Umukoro *et al.* [42], MJ (1, 5, 10 mg/kg, intraperitoneally [i.p.]) had a dose-dependent decrease in aggressive behaviors in resident-intruder and isolation-evoked paradigms (both measures offensive aggression) in mice. Although MJ has an anti-aggressive activity, it, however, does not impair the defense mechanism of the animals. These findings suggest the therapeutic usefulness of MJ as an anti-aggressive agent. Its ability to maintain the defense mechanism in animals suggests that it could be a better therapeutic approach to aggressive behaviors than antipsychotics and high doses of benzodiazepines which tends to impair the defensive mechanisms of organisms [43]. Of all the neurochemicals associated with aggressive behaviors, reduced 5-HT has been recurrently linked with aggression by numerous authors [43,44]. This hypothesis was further proven using a 5-HT_1 knockout rodents [40-46] (Table 1).

Memory/Cognitive Enhancement

MJ is used extensively in aromatherapy as a therapeutic agent for memory dysfunction [9]. In a study conducted by Umukoro *et al.* [22], intraperitoneal injection of MJ (25, 50, and 100 mg/kg) improved memory performance in mice exposed to UCMS. MJ was further shown to reverse UCMS-induced neurodegeneration in the sub-granular zone of the dentate gyrus and the pyramidal layer of the CA3 [22]. These learning and memory associated regions of the brain have been reported to exhibit loss of dendritic spines [47] and a reduced number of synapses [48] following UCMS. The results of the study established that UCMS produced the death of neuronal cells in the pyramidal layer of the CA3 and the sub-granular zone of the dentate gyrus of the hippocampus, the regions of the brain that plays vital roles in learning and memory [22].

Thus, a decrease in hippocampal density may lead to loss of memory function [49]. Previous clinical studies have linked reduced hippocampal volume to memory and cognitive impairment in patients with Alzheimer's disease (AD) [49,50]. Thus, oxidative stress-mediated hippocampal neuronal degeneration highlights memory impairment due to chronic stress. However, there are suggestions that compounds with a neuroprotective property may be of benefits in chronic stress-induced cognitive deficits and other neuropsychiatric disorders [51,52]. In another study, Eduviere *et al.* [19] used the passive avoidance paradigm to evaluate the influence of MJ on rat memory. This model uses aversive stimuli associated with fear as a condition for learning and memory acquisition [53,54]. This model assesses both the role of the hippocampus in memory [55] and the amygdala in fear-conditioned learning and memory [56]. It tests the ability of rodents to suppress motor activities to avoid an aversive event, which is dependent on the capability of the organisms to recall the unpleasant experiences [19]. The anti-amnesic activity of MJ was demonstrated using a passive avoidance task. MJ increased the latency period indicating an increase in the ability to retain and retrieve a memory. This test also demonstrated the mitigating effect of MJ pre-treatment on scopolamine-induced memory deficit. The test also demonstrates the attenuating effect of MJ on liposaccharide-induced amnesia. These findings further support the hypothesis that MJ has a positive effect on retention and retrieval of memory and that it plays a vital role in fear-conditioned memory. In different behavioral studies conducted by Umukoro and Eduviere [21] and Eduviere *et al.* [20] using the Y-maze paradigm, MJ attenuated memory deficits induced by lipopolysaccharide by increasing the alternation behavior of mice. The Y-maze is used to access spatial working memory, which is usually impaired in patients with AD. Therefore, heightened spatial working memory following MJ pretreatment indicates the anti-amnesic and memory-enhancing activity of MJ. Eduviere *et al.* [20] also used the object recognition test to assess the effect of MJ on the recognition memory of mice. The results showed that MJ significantly improved memory and attenuated scopolamine-induced memory impairment [20]. UCMS-induced memory dysfunctions were also attenuated by MJ via other mechanisms including Nrf2 expressions, antioxidant and monoaminergic systems [57].

Antipsychotic

Psychosis is a form of mental illness characterized by abnormal behaviors with little or no touch with reality [58]. It is characterized by multiple symptoms affecting thoughts, emotion, perception, and volition. It is a severe form of mental illness affecting the quality of life of the affected individuals [17]. Although pharmacological interventions have been the backbone of treatment of the disease, the use of antipsychotic drugs has certain limitations. These include the incidences of poor adherence, limited responses, and other incapacitating outcomes [59]. More notably, these drugs have failed to alter the course of the disease but are known to only provide symptomatic relief [17]. Likewise, the associated negative symptoms and memory deficits are not relieved by the antipsychotics [60-62]. Thus, the need to search for new drugs, especially agents with potential memory-enhancing effects as alternative treatments for psychotic disorders. Annafi and colleagues [17] adapted the bromocriptine-induced and ketamine-induced stereotypes as models to screen for the antipsychotic-like effect of MJ. It was reported that MJ demonstrated reduced stereotyped behaviors such as persistent sniffing, chewing, intense licking and head movements in mice, suggesting the antipsychotic-like property of MJ [17] (Table 1).

Anti-stress

Increasing the prevalence of physical, biological, or psychological stressors lead to an increase in stress and subsequently a rise in dyshomeostasis [63,64]. Organisms normally respond to acute stress by adapting to the changes in their environment. However, prolonged stress leads to illness or cell damage. Prolonged stress has been implicated in a variety of diseases such as hypertension, immune dysfunction, cancer, and several neurodegenerative disorders [23,64]. Adaptogens are a classified group of substances with the ability to improve the mental and physical performances of organisms during exposure to stressful stimuli [65]. Numerous studies have employed behavioral, and biochemical techniques to demonstrate the anti-stress property of MJ [22,23]. MJ decreased the immobility time in FST and increased the latency to convulsion in the hypoxia test in mice exposed to acute stress [23]. MJ was shown to reduce the level of corticosterone secretion in stressed mice indicating its adaptogenic-like property. Corticosterone induces brain damage by in-

creasing the intracellular level of oxidative stress. Chronic stress is known to trigger corticosterone release via the hypothalamic-pituitary-adrenal axis. This finding is further backed up by an increase in the adrenal gland and liver size which was noticed in UCMS-induced rats. Increased corticosterone levels can cause further damage via oxidative stress [50,66] and neuroinflammation [67]. MJ also decreased and increased the levels of malondialdehyde (MDA) and glutathione (GSH) which were originally increased and reduced respectively in the brains of mice exposed to UCMS. MJ subsequently attenuated the increased oxidative level induced by UCMS [18,22,57]. MJ has also been shown to possess anti-fatigue property via its effect on the enzymes of the purinergic system [68].

MECHANISM OF MJ MODULATORY ACTIVITIES

Antioxidant

Oxidative stress has been implicated as a mechanism of cell damage and by extension, neuronal cell death. Oxidative stress occurs when there is a higher level of reactive oxygen species compared to antioxidants in the body. Various environmental stressors trigger the production of free radicals, which initiate a series of events leading to neurodegeneration [69,70]. Also, the inflammatory mediators released by injured neural cells additionally augment the production of free radicals resulting in neuronal cell death [69]. MJ amongst other adaptogens exhibits antioxidant property (Fig. 2). This was seen in studies where MJ decreased and increased the levels of MDA and GSH which were originally increased and reduced respectively in the brains of UCMS-treated mice [20,22,57,71]. In another study by Shanmugarajan [72],

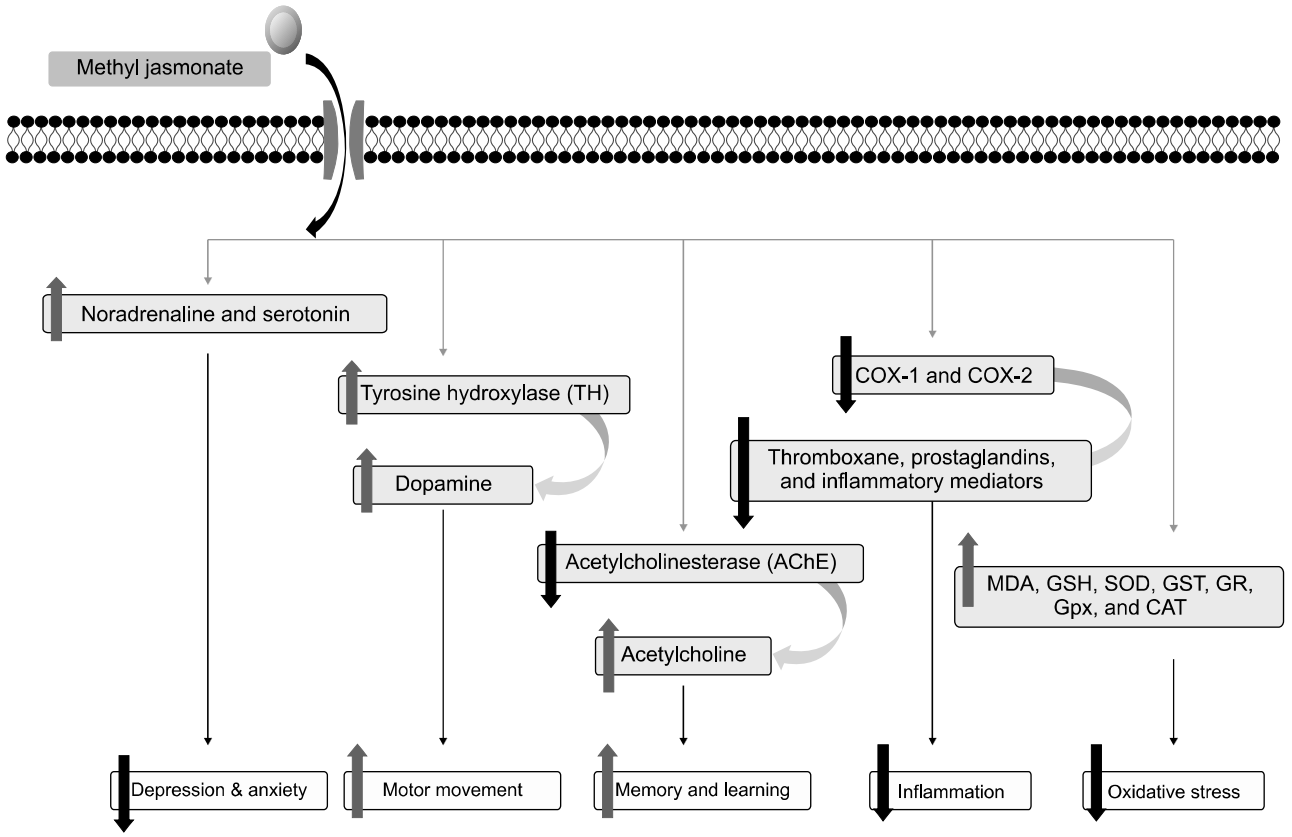

Fig. 2. Schematic diagram showing the molecular mechanisms underlying the therapeutic potential of MJ in neurological disorders.
MJ, Methyl jasmonate; MDA, malondialdehyde; GSH, glutathione; SOD, superoxide dismutase; GST, glutathione-S-transferase; GR, glutathione reductase; GPx, GSH Peroxidase; CAT, catalase.

MJ significantly increased the activity of superoxide dismutase, glutathione-S-transferase, glutathione reductase, GSH Peroxidase, and catalase compared to the lipopolysaccharide-induced group, which further confirmed its antioxidant activity.

Inflammatory Biomarkers

Injured tissues undergo inflammatory response to limit the level of damage and enhance healing [73]. Inflammation is mostly the underlying cause of pain. And also manifest in other forms such as redness, warmth, swelling, and loss of functions [74]. Anti-inflammatory drugs are designed to inhibit the action of cyclooxygenase enzymes (COX-1 and COX-2). These enzymes are responsible for the formation of prostaglandins, which are potent mediators of inflammation [75]. Chronic stress has also been linked to an increase in the release of pro-inflammatory cytokines, neuroinflammation, and subsequently depressive-like behaviors [66]. These inflammatory markers have been linked to the pathogenesis of neurodegenerative diseases such as Alzheimer's disease [76,77]. Interleukin-1β (IL-1β) for example, is a well-known powerful pro-inflammatory cytokine with pleiotropic functional and behavioral functions [78,79]. IL-1β activates microglia and increases blood-brain barrier permeability, which promotes leukocyte permeation and upregulation of other pro-inflammatory molecules such as prostaglandin E2 (PGE2) and TNF-α [78,79]. Clinical studies have linked elevated brain levels of inflammatory biomarkers in AD patients [78,80]. Also, a causative connection between IL-1β brain levels and memory deficits has been well reported in numerous literature [80,81]. Due to the structural similarity between MJ and anti-inflammatory prostaglandins, investigations are being carried out to ascertain its therapeutic potential for inflammatory disorders [5]. Lee *et al.* [82] and Dang *et al.* [4] investigated the anti-inflammatory potential of MJ in cultured cells. The inhibition of the NF-κB signaling pathway led to the confirmation of the anti-inflammatory potential of MJ [82]. A similar pathway was observed in plants resulting from an increased level of jasmonate secretion following infections or injuries [1]. Umukoro and Eduviere [21] further examined the effect of MJ on inflammatory biomarkers in mice brain following lipopolysaccharide injection. In that study, MJ reduced the level of PGE2, inflammatory cytokines (TNF-α and IL-1β), COX2, iNOS, and NF-κB. These findings further suggested the anti-neuroinflammatory activity of MJ. MJ (5−20 mg/kg, i.p.) reduced the increased level of TNF-α in the brains of mice subjected to UCMS. MJ was also suggested to mitigate UCMS-induced anti-depressive behaviours via its inhibiting of oxidative stress and neuroinflammation [18]. Previous studies have also demonstrated the capability of MJ to silence genes involved in the synthesis of proinflammatory cytokines [4,83].

Neurotransmitter Regulation

Neurotransmitters are vital biochemical molecules that regulate behavioral and physiological functions in the CNS and PNS. Consequently, the study of neurotransmitters in biological samples has immense clinical and pharmaceutical importance [84]. MJ, an adaptogen, has been shown to regulate the synthesis and action of various neurotransmitters (Fig. 2). It enhances both serotonergic and noradrenergic transmissions [37]. It acts as a 5-HT_1 receptors agonist, thereby enhancing serotonergic neurotransmission [42]. Studies incriminating noradrenaline and serotonin in the pathogenesis of depression are detailed in both preclinical and clinical pieces of literature [2,33,34,36,85]. Various agents such as MJ with antidepressant activity in rodents increase the extracellular availability of amines in the brain [37,86]. Although the exact mechanism of action of MJ needs to be explored before coming to any conclusions on its mechanism of action, preliminary investigations suggest that its antidepressant-like effect may involve serotonergic and noradrenergic mechanisms [37]. Additionally, MJ significantly reduces acetylcholinesterase activity in mice brains increasing brain-level acetylcholine. Acetylcholine is an essential neurotransmitter in the process of learning and memory [20,87,88]. There is also evidence of modulation of the monoaminergic system vis-à-vis adrenaline, dopamine, serotonin, and monoamine oxidase by MJ [57]. MJ also increases the immunoexpression of tyrosine hydroxylase in the midbrain and striatum of rotenone-induced rats [89]. Reduced tyrosine hydroxylase expression has been implicated in dopamine depletion [90,91]. These changes suggest the regulating activity of MJ on neurotransmitter synthesis and activity in the CNS.

Neuroregeneration

A key obstacle for neural repair is the weak re-

generative ability of injured neurons, although the neonatal brain has more capacity for recovery than the adult brain. There are various reports on the role of some agents in promoting the regeneration of injured and degenerating neurons in the brain [92]. In a study by Umukoro *et al.* [22], MJ reduced the extent of neuronal damage in the pyramidal layer of the CA3 and the sub-granular layer of the dentate gyrus of mice subjected to UCMS [22]. They also quantified the neuronal cell population and reported increase neuronal density in the pyramidal layer of the CA3 and the sub-granular layer of the dentate gyrus in UCM-stressed mice following treatment with MJ [22]. Similar results were seen in a study by Eduviere *et al.* [93] where MJ improved neuronal structure and density in the prefrontal cortex and CA1 of mice treated with lipopolysaccharide [93]. In another study, MJ reduced cytoarchitectural alterations and loss of neurons in the striatum of rotenone-treated rats [89]. MJ also significantly reversed structural alterations of the dendritic spine and improved dendritic density in rotenone-treated rats [89]. Additionally, it also reduced the loss of dopaminergic neurons in the midbrain of rotenone-rats [89].

THERAPEUTIC POTENTIAL OF MJ IN NEURODEGENERATIVE DISEASES

Alzheimer's Disease

Progressive memory loss is a major feature of Alzheimer's disease, a neurodegenerative disorder. Its prevalence increases with age [94]. Its pathohistological hallmark includes neurodegeneration of brain regions associated with learning and memory like the hippocampus [94]. It is also associated with the loss of cells involved in the cholinergic pathway. Brain cells are highly susceptible to the damaging effect of reactive oxidative species (ROS) due to their elevated rate of utilizing oxygen and reduced antioxidant defense systems [20]. ROS initiates lipid peroxidation, which triggers neuronal degeneration especially in the cholinergic system and subsequently Alzheimer's disease [20]. The role of oxidative stress in AD is confirmed by increased levels of MDA in post-mortem brains [95-97]. The potential of MJ as a therapeutic agent for the treatment of Alzheimer's disease has been explored by numerous studies. MJ attenuated memory deficits induced by lipopolysaccharide by increasing the alternation behavior of mice subjected to the Y-maze test [21]. The Y-maze is used to access spatial working memory, which is usually impaired in AD. Therefore, enhanced spatial working memory following MJ treatment indicates its anti-amnesic and memory-enhancing activity. The histomorphological study by Umukoro *et al.* [22] demonstrated the ameliorative effect of MJ on UCMS-induced neuronal damage in the pyramidal and sub-granular regions of CA3 and DG respectively mice [22]. Neuronal damage in the hippocampus has been frequently linked to AD. MJ also attenuates the depleting population of hippocampal neurons in UCMS-subjected mice, further proving its neuroprotective effect. Since several neurochemical studies have been linked to neuroinflammation with AD pathogenesis [76,77]. Umukoro and Eduviere [21] accessed the therapeutic potential of MJ for AD by examining various neuroinflammatory biomarkers in lipopolysaccharide-treated mice. Their results showed a reduction in the level of PGE2, inflammatory cytokines (TNF-α and IL-1β), COX2, iNOS, and NF-κB following MJ treatment. Inhibiting factors involved in the inflammatory process could be a useful therapeutic approach for this disorder [21]. Thus, it is safe to infer that the ability of MJ to overturn IL-1β, PGE2, and TNF-α levels suggests an important role in enhancing memory. Also, MJ suppressed the expression of Aβ1−42 in the brain of mice treated with lipopolysaccharide, which suggests memory-enhancing property. An increased level of Aβ1−42 induces neuronal death, characterizing the pathological hallmark of AD [98,99]. Additionally, excessive accumulation of Aβ in the brain further exacerbates oxidative stress and increases the inflammatory responses in progress, thus spreading neuroinflammation that results in progressive neurodegeneration and loss of cognitive functions in lipopolysaccaride-treated animals [77,98-100]. The attenuating effect of MJ on the level of Aβ signifying its anti-amyloid genesis-like effect. It is also imperative to note that MJ is generally safe for use in humans, as it forms a major component of our diets like fruits and vegetables, thereby making it a promising therapeutic agent for AD [5].

Parkinson's Disease

Parkinson's disease (PD) is the second most popular neurodegenerative disease and is generally believed to primarily affect the dopaminergic neurons of the substantia nigra [101,102]. The pathological progression of PD is frequently believed to be a simple process that in-

cludes selective degeneration of the nigrostriatal pathway and a concurrent depletion in striatal dopamine [103]. This model has directed the development of the present therapies for PD and the investigations for new ones. Most of these focus on alleviating motor symptoms rather than modifying the disease [103]. The recognition of several non-motor symptoms of PD related to the degeneration of non-dopaminergic transmitter systems [104] has made these therapies less efficient. These non-motor symptoms include olfactory dysfunction, sleep abnormalities, gastrointestinal dysfunction dysfunction, anxiety, depression, and pain [105]. This, together with the fact that medications like levodopa lose efficiency and cause dyskinesias and behavioral anomalies in many patients, calls for the development of an efficient therapy that targets both the motor and non-motor pathway. Although there are numerous studies on the ameliorative potential of MJ on various non-motor symptoms associated with PD, it is however not certain if these signify a therapeutic effect of MJ against Parkinson's disease. MJ attenuated the anxiety-like effect of UCMS in mice [22]. This is consistent with the result seen in a study by [18] where MJ (5−20 mg/kg, i.p.) improved spontaneous muscle activities which were initially decreased by UCMS in mice. MJ reduced the immobility period in FST and TST [37]. The effect of MJ on motor symptoms was studied by Alabi *et al.* [89]. It reversed rotenone-induced deficits in locomotor activity and rearing behavior in rats. It significantly inhibited rotenone-induced dopamine reduction in the striatum, midbrain, and prefrontal cortex and increases the expression of tyrosine hydroxylase and dopamine in the striatum and the substantia nigra of rotenone-induced rats [89]. With the loss of dopaminergic neurons, the local supply of dopamine has been associated with motor deficits [106]. MJ also improves histomorphology by preventing and reverting neuronal damage in the SN and striatum of rotenone-induced rats. It preserved the dendritic network in the substantia nigra and striatum of rotenone-induced rats [89].

CONCLUDING REMARKS

The pathogenesis of many neurologic disorders and neurodegenerative diseases have causative associations with oxidative stress, inflammation, and neurotransmitter dyshomeostasis. These disorders exhibit symptoms such as anxiety, depression, aggression, psychosis, and memory impairment. Recent evidence highlighting the therapeutic potential of MJ in managing these symptoms and by extension, neurological disorders are reviewed. Reports from different studies reported MJ to possess the abilities to act as an antioxidant, anti-inflammatory, anti-neurogenerative, and as a neurotransmitter-regulating agent. Its neuroprotective and anti-neurodegenerative properties in the rodents' brains were also implicated in Alzheimer's and Parkinson's disease. Although various studies are highlighting the neuroprotective property of MJ, none has examined the exact mechanism of MJ. Therefore, further understanding of the mechanism by MJ acts will give better insight into modeling MJ as a targeted therapy for managing the diseases of the brain.

■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Concept and design: Oritoke Modupe Aluko, Omamuyovwi Meashack Ijomone. Manuscript drafting: Oritoke Modupe Aluko, Joy Dubem Iroegbu. Critical revision: Omamuyovwi Meashack Ijomone, Solomon Umukoro.

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