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REVIEW

Demethyleneberberine, a potential therapeutic agent in neurodegenerative disorders: a proposed mechanistic insight

Priyanka Saklani[1] · Heena Khan[1] · Thakur Gurjeet Singh[1] · Saurabh Gupta[1] · Amarjot Kaur Grewal[1]

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Abstract

Introduction Neurodegenerative disorders are a diverse variety of diseases that can be distinguished from developing degeneration of neurons in the CNS. Several alkaloids have shown mounting effects in neurodegenerative disorders, and berberine is one of them. Demethyleneberberine is a metabolite of berberine that has better blood-brain barrier crossing capacity. Demethyleneberberine possesses anti-inflammatory, anti-oxidant, and mitochondrial targeting properties. However, neither the pharmacological action nor the molecular mechanism of action of demethyleneberberine on neurodegenerative disorders has been explored yet.

Materials and methods A systematic literature review of PubMed, Medline, Bentham, Scopus, and EMBASE (Elseveier) databases was carried out with the help of keywords like "Demethyleneberberine; neuroinflammation; oxidative stress; Neuroprotective; Neurodegenerative disorders" till date.

Conclusion This review focus on the neuroprotective potential of demethyleneberberine in neurodegenerative disorders by attenuating different pathways, i.e., NF-κB, MAPK, and AMPK signalling.

Keywords Demethyleneberberine · Neuroinflammation · Oxidative stress · Neuroprotective · Neurodegenerative disorders

Abbreviations

DMB	Demethyleneberberine
BBR	Berberine
NDDs	Neurodegenerative disorders
CNS	Central nervous system
ROS	Reactive oxygen species
Ca^{2+}	Calcium
Htt	Huntingtin
NAFLD	Non-Alcoholic Fatty Liver Disease
ALD	Alcohol liver disease
MDA	Malonaldehyde
GSH	Glutathione
ECM	Extracellular matrix
MMPs	Matrix metalloproteinases
TIMPS	Tissue inhibitors of metalloproteinases
TGF-1	Transforming growth factor-1
CYP2E1	Cytochrome P450 2E1
HIF-1α	Hypoxia-inducible factor 1-alpha
iNOS	Inducible nitric oxide synthase
qPCR	Quantitative polymerase chain reaction
IHC	Immunohistochemical
TNF-α	Tumour necrosis factor-alpha
CO	Cyclooxygenase
IL	Interleukin
iNOS	Inducible nitric oxide synthase
NFT	Neurofibrillary tangles
TAA	Thioacetamide
MAPK	Mitogen-activated protein kinase
AMPK	AMP-activated protein kinase
MAO-B	Monoamine oxidase-B
UTI	Ulinastatin
CYP2E1	Cytochrome P450 2E1
MDA	Malondialdehyde
INF-γ	Interferon-gamma

Introduction

Neurodegenerative disorders (NDDs) affect the central nervous system (CNS) and are distinguished by the continuous degeneration of nerve cells. Neuronal changes impair their function and result in the demise of the cell. This is because neurons are unable to regenerate on their subsequent neural

✉ Thakur Gurjeet Singh
gurjeet.singh@chitkara.edu.in; gurjeetthakur@gmail.com

[1] Chitkara College of Pharmacy, Chitkara University, Rajpura, Punjab 140401, India

degeneration or damage [1]. The underlying cause of NDDs like Amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), Epilepsy, Huntington's disease (HD), Alzheimer's disease (AD), and stroke has been postulated to be oxidative damage [2]. Reactive oxygen species (ROS) can harm proteins, membrane polyunsaturated fatty acids, and nucleic acids resulting in the loss of membrane integrity, lipid peroxidation, a decrease in the potential of mitochondrial membrane, and an increase in plasma membrane's permeability to Ca^{2+} [3]. NDDs remain incurable and are notably increasing morbidity/mortality rates in developing countries, with a similar trend anticipated in developing countries as more statistics become available. The available treatments for NDDs are solely focused on disease management; actual treatment has yet to be examined [4]. Synthetic medications are used to treat NDDs and a variety of other chronic conditions, but they are not without negative effects such as extrapyramidal reactions caused by drugs like reserpine, metoclopramide and phenothiazines; riluzole can cause nausea, diarrhoea and rarely hepatotoxicity etc. Most drugs show their action by ameliorating the symptoms of disease, due to this the phytochemicals have gotten a lot of attention from researchers because of minimal side effects and good BBB crossing ability. Treatment with free radical scavengers or antioxidants targeted at reducing pro-oxidant synthesis or enhancing antioxidant defences [2, 5]. Since ancient times, phytomedicines or plant-derived components such as flavonoids and alkaloids have treated NDDs. They can be the most productive management and therapeutic agents for minimizing the critical characteristics of NDDs like amyotrophic lateral sclerosis, AD, PD, HD, epilepsy, and stroke [6]. Numerous phytochemicals exhibit neuroprotective activity, and among them, alkaloids are one of the most effective agents against NDDs. Plants, fungi and marine sponges all produce alkaloids which are a type of secondary metabolite. They are well-known as a trustworthy remedy for cancer, diabetes & therapeutic interventions for NDDs. Berberine (BBR) has been used in the Chinese and Ayurvedic systems of medicine for approximately 3100 years and can be obtained from various plants, namely Coptis Chinensis (golden thread or copies), Berberis vulgaris (barberry), Berberis aristata (tree turmeric) and Hydrastis canadensis (goldenseal)[6]. BBR alkaloids are a class of structurally disparate protoberberine compounds that comprise but are not limited to demethyleneberberine (DMB), jatrorrhizine, columbamine, palmatine and berberine. Berberine alkaloids are quaternary ammonium salts that spread a tetracyclic skeleton densely packed with hydroxyl oxidation states at locationsC2, C3, C9 and C10 [7]. BBR has been shown to improve pathology and symptoms related to AD, PD, HD, ALS, stroke and epilepsy [8–14].

Additionally, in various diabetes models of the animal, BBR has been proven to downregulate the pro-inflammatory cytokines and oxidative stress markers [15, 16]. DMB has been proposed to be the central intermediary in the biogenesis of berberine alkaloids. It was previously believed that the biosynthesis of berberine alkaloids began with the evolution of demethyleneberbeine from berberine. DMB was then methylated to form other types of berberine alkaloids [17, 18]. Due to less availability of literature on the neuroprotective potential of DMB, it was hypothesized that DMB possesses all the properties of berberine including neuroprotective potential, as DMB is a metabolite of berberine.

This review focuses on demethyleneberberine's neuroprotective potential in AD, PD, HD, ALS, epilepsy, and stroke via modulation of NF-κB, MAPK, and AMPK signalling.

Methodology

A systematic literature review of PubMed, Medline, Bentham, Scopus, and EMBASE (Elseveier) databases was carried out with the help of keywords like "Demethyleneberberine; neuroinflammation; oxidative stress; Neuroprotective; Neurodegenerative disorders" from 1985 to November 2021. The review was conducted using the above keywords to collect the latest articles and understand the nature of the extensive work done on Demethyleneberberine: Mechanistic and molecular approach in neurodegenerative disorders (Fig. 1).

Pathophysiology of neurodegenerative disorders in a nutshell

All neurodegenerative diseases are triggered by the unfolding of proteins, leading to the synthesis of "β-structures" and a pathological tendency for neuronal cell aggregation. This is a characteristic of tau protein in AD and various tauopathies linked with tau unfolding, huntingtin (htt) in Huntington's disease, and α-synuclein in PD. These unfolding events in proteins are molecular events that particularly initiate various NDDs. Notably, such episodes take place due to neuroinflammatory cascades [19]. Furthermore, based on the molecular pathogenesis, these diseases share a lot of similarities, and proteinopathy is one of them i.e. abnormal accumulation of misfolded proteins (accumulation of amyloid-beta (Aβ) in AD, α-synuclein PD, HTT in HD and p-TDP-43 aggregation in ALS) [20]. Normal ageing, dementia, high blood pressure, stroke, obesity, systemic and local infections, brain injury and environmental conditions all activate astrocytes, neurons and microglia in the brain, causing neuroinflammation. Immune & inflammatory cells in the brain, i.e. T-cells and mast cells, are also activated by these substances. Microglia & inflammatory cells that are activated trigger the discharge of cytokines and neurotoxic mediators, furthermore enhancing the expression of inflammatory receptor proteins in the brain. These inflammatory

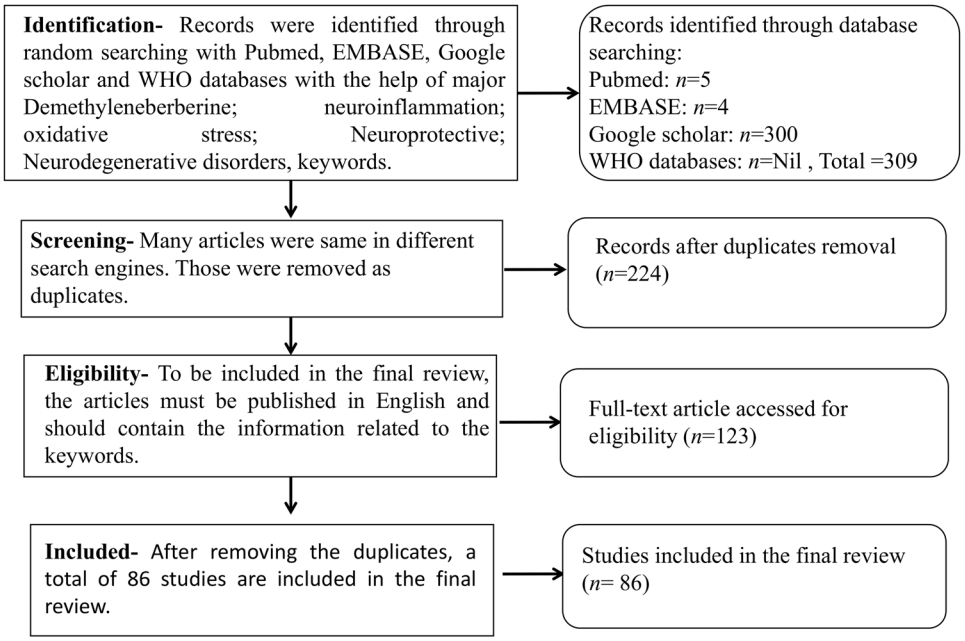


Fig. 1 Flowchart of the methodology

mediators and increased protein expressions exacerbate neuroinflammatory processes and neurodegeneration, leading to the progression of neurodegenerative disorders [21].

Alzheimer's brain is characterized by widespread cortical atrophy induced by dendritic tree shrinking and degeneration of the cholinergic axonal arborization. Microscopically, affected areas exhibit neurofibrillary tangles and amyloid-beta peptide deposits (senile plaques) [22, 23].

Additionally, AD is distinguished by neuroinflammation, triggered by the activation of astroglia and microglia [24].

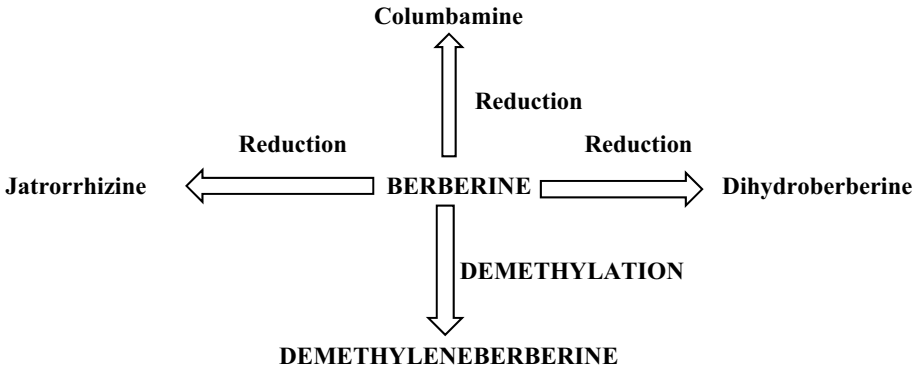
In PD, the deposition and accumulation of α -synuclein, a presynaptic neuronal protein, drives its pathogenesis. The bioenergetic impairment, oxidative stress and anomalous protein regulation, are all linked to the aetiology of PD [24]. HD can be defined as the progressive loss of nerve cells in the stratum cerebral cortex and the selective neuronal dysfunction caused by various neuronal cell death mechanisms, including poor energy metabolism, apoptosis, oxidative stress, and excitotoxicity [25]. Microglia cells are activated macrophages in the brain which produce an array of pro-inflammatory cytokines in the presence of Htt [18].

ALS is catalyzed by a complex array of factors, including endoplasmic reticulum stress, inflammation, dysregulated endosomal trafficking, genetic susceptibility, oxidative stress, transcription and RNA processing, excitotoxicity, and mitochondrial dysfunction, and apoptosis [26]. A stroke causes an abrupt impairment of the function of the brain due to disruption in the cerebral blood supply. When the formation of plaques occurs along with the injured vessel, the intima is eroded, leading to the formation of thrombosis in intracranial arteries. According to studies, cerebral ischemia activates the NMDA receptor, resulting in the oxidation of vital cellular components and aggregation of ROS. Additionally, this alters signalling pathways, resulting in cellular damage and death [1]. Epilepsy's primary aetiology is currently an imbalance between inhibitory and excitatory neurotransmission, oxidative stress, and inflammation. Increased pro-inflammatory substances may result in the excessive loss of neuronal excitation, affecting GABA receptors. The neuronal excitability can be enhanced due to the alteration of calcium currents because of oxidative stress [27].

According to the literature available [21–26], it is clear that neuroinflammation, oxidative stress, and mitochondrial dysfunction has a major role in the pathophysiology of NDDs. Due to berberine's antioxidant and neuroprotective properties [8–14], its metabolite, demethyleneberberine (DMB), could be utilized to decrease NDDs, as DMB is more effective than BBR at crossing the "blood–brain barrier" and employing its therapeutic effect.

Mechanistic approach of demethyleneberberine

DMB (9,10-dimethoxy-5,6-dihydroisoquinolino [2,1-b] isoquinolin-7-ium-2,3-diol) is a novel cationic antioxidant having the molecular formula C ^{19}H ^{18} NO $^{4+\cdot}$ DMB is one of berberine's primary metabolites and was found to be the crucial intermediate in the berberine alkaloids biogenesis [17]. DMB is known to have anti-oxidant [28], anti-inflammatory [29] and anti-fibrotic [30] properties which indicate that DMB may have therapeutic potential in neurogenerative disorders because the properties possessed by DMB have proven to be neuroprotective in NDDs.



The above flow chart indicates that the reduction of berberine leads to the formation of Columbamine, Dihydroberberine and Jatrorrhizine whereas demethylation of berberine results in the formation of Demethyleneberberine.

Demethyleneberberine as a potential anti-oxidant

Ageing and numerous brain disorders are thought to be regulated by oxidative stress. Oxidative stress occurs when the balance between the level of antioxidants and the formation of ROS is remarkably disrupted [31]. Through modulation of the function of biomolecules, ROS contributes to neurodegeneration development [32]. ROS can oxidize various substrates in cells, resulting in protein, DNA, RNA oxidation, and lipid peroxidation [33]. DMB contains two exposed phenolic hydroxyl groups, implying that it may possess antioxidative properties to combat the "second hit" (oxidative stress and inflammation), as previously demonstrated in studies that DMB reduced Alcoholic Liver Disease (ALD) via mitochondria-targeted antioxidative effects [28]. In chronic ethanol-fed mice, DMB inhibited iNOSs, CYP2E1, and HIF-1α, which resulted in oxidative stress and restored sirtuin 1/AMP activated protein kinase/PPARGC1A pathway-associated fatty acid oxidation ameliorated hepatic lipid peroxidation and macrosteatosis. According to the study, DMB treatment significantly reduced the oxidative damage caused by Non-Alcoholic Fatty Liver Disease (NAFLD), as measured by reducing the lipid oxidative product malonaldehyde (MDA) [34]. This demonstrated that DMB could alleviate oxidative stress and thus hepatitis caused by Con A. In another study, pre-treatment with DMB emerged to reduce MDA accumulation and increase serum Albumin and hepatic GSH levels [35]. As a result of these findings, it has been concluded that DMB possesses anti-oxidant properties.

Demethyleneberberine as an anti-fibrotic agent

The damaged neurons in the CNS can not regenerate and scar-forming cells like inflammatory immune cells, astrocytes, endothelial cells, and stromal fibroblasts can linger for a prolonged time in the brain. New evidence suggests that a fibrotic reaction is involved in persistent CNS injuries similar to those seen in neurodegenerative disorders, where fibrosis, as well as inflammation, promote deterioration. The essential pathogenic feature of fibrosis is the subsequent aggregation of proteins in the extracellular matrix (ECM) [36]. ECM and MMPs are essential moderators of neuroplasticity, cognition and may play a role in various neurological disorders [37]. In fibrotic tissue, Collagen type I is an extracellular matrix component, whereas serum hydroxyproline is an indicator of the metabolism and content of collagen (Fig. 2). During fibrogenesis, the interpretation of ECM proteases, for example, MMPs and TIMPs, rise. Additionally, the ECM contains growth factors, including TGF β-1, that modulate activation and proliferation. In thioacetamide (TAA)-induced hepatic fibrosis, qPCR and Immunohistochemical (IHC) analysis revealed that DMB inhibits collagen synthesis and increases collagen degradation by inhibiting TGF-1-Smad signalling, decreasing tissue inhibitors of MMP (TIMPs) and matrix metalloproteinases (MMPs) expression [30]. This suggests that DMB may be able to ameliorate hepatic fibrosis by inhibiting HSC activation. As a result, DMB can act as an anti-fibrotic agent.

Demethyleneberberine as an anti-inflammatory agent

Inflammation is becoming more recognised as a key factor in neurodegenerative disorders. Microglia are known as the primary effectors in the central nervous system's

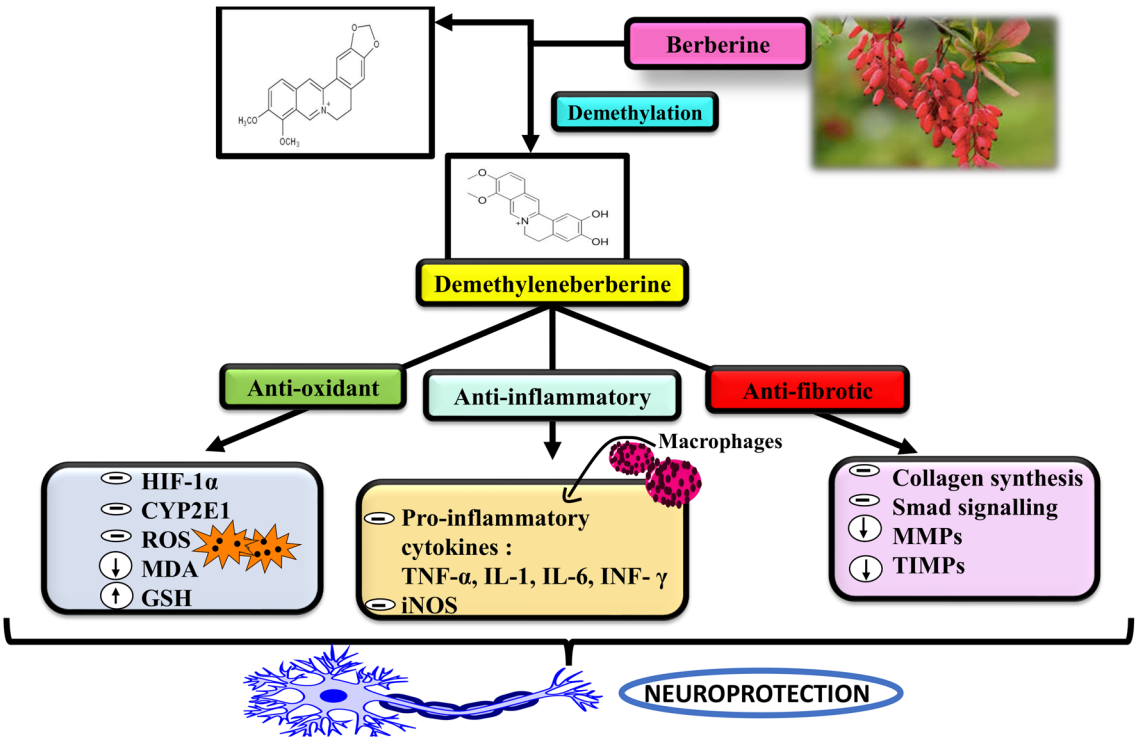


Fig. 2 Pictorial representation of Demethyleneberberine (DMB), a metabolite of Berberine showing three different properties, i.e., anti-oxidant, anti-inflammatory, and anti-fibrotic. *HIF-1α* hypoxia-inducible factor 1-alpha, *CYP2E1* cytochrome P450 2E1, *ROS* reactive oxygen species, *MDA* malondialdehyde, *GSH* glutathione, *TNF-α* tumor necrosis factor alpha, *IL-1* interleukin-1, *IL-6* interleukin-6, *INF-γ* interferon gamma, *iNOS* inducible nitric oxide synthase, *MMPs* matrix metalloproteinases, *TIMPs* tissue inhibitors of metalloproteinases)

inflammatory process and their activation leads to the increased expression of the cell surface antigens and discharge of pro-inflammatory cytokines, i.e., TNF-α, interleukin-6, interleukin-12, cyclooxygenase-2, and chemokines [38]. The formation of free radicals and excitotoxicity results in extensive brain damage leading to neuronal death occurs due to the release of pro-inflammatory cytokines [39]. In NDDs, where astrocytes and microglia are the primary inflammatory cells, therapeutic approaches aim to modulate the innate immune system's sensor/transducer/effector functions, i.e., TLRs, NF-κB, and TNF-α, respectively [40]. It was noted that, in the autoimmune hepatitis study, the expression and release of IFN-γ and TNF-α were significantly increased and were expectedly reversed in the DMB pre-treatment group. This study implicates that the expression of pro-inflammatory cytokines can be regulated by NF-κB signalling, leading to the pathogenesis of inflammatory liver diseases [35]. According to another study, DMB inhibited pro-inflammatory cytokine's production, namely IL-6, TNF-α and decreased IFN-c levels in mice splenocytes in mice with inflammatory bowel disease [29]. These findings demonstrate that DMB can act as an anti-inflammatory agent (Table 1).

Molecular approach of demethyleneberberine in neurodegenerative disorders

Various studies have found that demethyleneberberine inhibits its oxidative stress, neuroinflammation, mitochondrial dysfunctions, and ROS/RNS by showing its action on NF-κB, AMPK, and MAPK [28–30] and modulation of these pathways has shown neuroprotective function in neurodegenerative disorders. So, it has been hypothesized that DMB might have the potential to attenuate various neurodegenerative disorders via attenuating NFκB, AMPK, and MAPK signalling pathways in the brain. The role of berberine in the neuroprotection of various neurodegenerative disorders also indicates the possibility of DMB having the same potential as it is a metabolite of berberine (Table 2).

Demethyleneberberine in Alzheimer's disease

AD is correlated with ageing along with two neuropathological events, i.e., the deposition of amyloid plaques (Aβ) in extracellular space & intracellular neurofibrillary tangles (NFT) [46]. It is a multifactorial disease that develops due to the interaction of genetic and environmental factors.

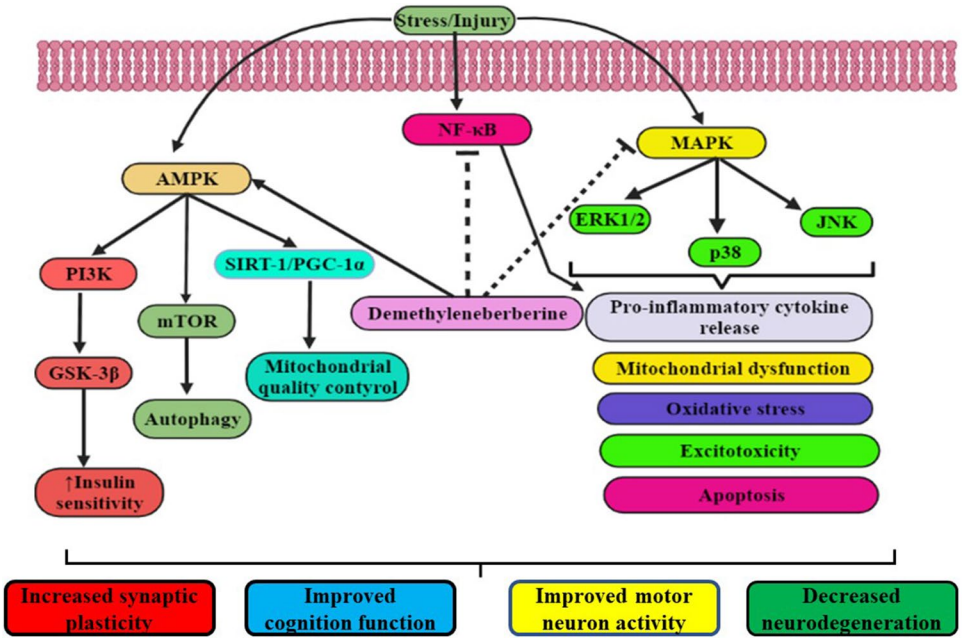


Fig. 3 The figure shows increased synaptic plasticity, decreased neurodegeneration, and improved cognition function & motor neuron activity via modulation of NF-κB, MAPK, and AMPK signalling pathway with Demethyleneberberine

Table 1 Table summarizing the neuroprotective role of berberine in neurodegenerative disorders

S. no.	Disease	Animal model	Outcome	References
1	Alzheimer's disease	Transgenic mouse model	Berberine provided neuroprotection in transgenic mice by regulating amyloid precursor protein processing (APP)	[41]
		Al-maltol induced Rabbit model	Anti-inflammatory characteristic of berberine chloride as well as suppression of acetylcholinesterase and to lesser extent inhibition of β- secretase that protects CNS cells in AD from oxidative stress and inflammation	[9]
2	Parkinson's disease	MPTP/P induced mice model	Berberine improved coordination and motor balance in PD by delaying the loss of dopaminergic neurons and also helped with short term memory problems by induction of apoptosis in the hippocampal region of the brain	[10]
3	Huntington's disease	Transgenic mouse models	Berberine improved the autophagy process in HD mice by reducing the accumulation of mutant htt and neurological symptoms	[42]
4	Amyotrophic lateral sclerosis	Cellular model	Berberine inhibited the production of insoluble TDP_43 aggregates by inhibiting the mTOR/p70S6K signalling pathway and activating the autophagic degradation pathway	[43]
5	Stroke	Gerbils model	Berberine treatment attenuated microglia activation & reactive astrogliosis. Berberine also increased the expression of Phospho-PI3K and Phosphor-Akt in the hippocampal region of ischemic gerbils	[44]
6	Epilepsy	Kainic acid-induced mice model, Maximal electroshock mice model, NMDA induced mice model, PTZ mice model	Berberine reduced the frequency of tonic hind limb extension and % mortality in the MES- induced seizures paradigm, as well as protecting mice from KA-induced clonic convulsions and death. Furthermore, berberine also protected mice from turning behaviour caused by NMDA induced mice model	[45]

Table 2 Table summarizing the list of protective effects of DMB in various diseases

S. no.	Property	Disease	Pathway involved	Conclusion	References
1	Anti-inflammatory and anti-oxidant	Non-alcoholic fatty liver disease	AMPK activation	DMB inhibits inflammation and oxidative stress in the liver, which results in the progression of non-alcoholic steatohepatitis	[34]
		Autoimmune hepatitis	Inhibition of NF-κB and MAPK signalling activation	DMB significantly inhibited inflammatory cytokines expression and downregulated the oxidative stress with the decrease of MDA and increase of GSH	[35]
		Inflammatory colitis	Inhibition of NF-κB signalling action	DMB markedly inhibited ROS production and pro-inflammation cytokines *in -vitro*	[29]
2	Anti-oxidant	Ethanol-induced Alcoholic liver disease	HIF- α and iNOS suppression	DMB decreased the oxidative stress and re-stored sirtuin 1/AMP-activated protein kinase/PPARGC-1a pathway–associated fatty acid oxidation	[34]
3	Anti-fibrotic	Thioacetamide-induced hepatic fibrosis	Inhibition of TGF-β1-Smad signalling	DMB inhibited the collagen synthesis and increased the degradation of collagen by blocking the TGF-β1 and reducing the expression of MMPs and TIMPs	[30]

Neuroinflammation is linked to Alzheimer's disease over the last decade. Today, nearly all drug treatments for AD are ineffective. There is a critical need for therapies that can help prevent and slow down the progress of Alzheimer's disease [47]. The primary impediment to developing AD drugs is unclear regarding the mechanisms underlying AD pathogenesis and pathophysiology. Presently, there are no drugs available that modify AD. As a result, neuroinflammation has been put forward as an alternative therapeutic target for preventing and treating AD [48]. Since berberine has shown therapeutic potential in various mice and rabbit models of Alzheimer's disease [41], it becomes possible that the metabolite of berberine; DMB can also have therapeutic potential. Given that the transcription factor NF-κB is required to express many pro-inflammatory cytokines. According to the literature, brain-permeable inhibitors of NF-κB signalling may be used to slow the progression of AD. Microglia, the brain's resident macrophages, stimulate the NF-κB signalling [49]. NF-κB performs as a transcription factor for various chemokines and cytokines, including interleukins, tumour necrosis factors, interferons, and lymphokines [50]. According to a study, DMB inhibited the NF-κB and MAPK signalling activation in con-A-induced autoimmune hepatitis, indicating the use of DMB in the treatment of autoimmune hepatitis [35]. DMB also alleviated colitis and inhibited inflammatory responses in mice in an in vivo study via inhibiting the NF-κB pathway [29]. In another study, DMB inhibited the NF-κB signalling in mice with thioacetamide (TAA)-induced hepatic fibrosis [30]. So, it can be proposed that in AD, DMB could be used as a neuroprotective agent as DMB has been proven to inhibit the NF-κB signalling, which contributes to neuroinflammation in AD. Numerous proteins have been recognized as possible targets for treating Alzheimer's disease. The p38 MAPK signalling has been considerably reviewed in recent years; extensive research into the pathophysiology of AD has revealed novel roles for p38 MAPK in the process of memory loss and cognitive decline [51, 52]. Evidence states that DMB inhibited MAPK signalling [35], so it can be suggested that DMB may play a significant role in reversing memory loss and cognitive decline associated with AD (Fig. 3). There is mounting evidence that AMP-activated protein kinase (AMPK) may have a wide range of neuroprotective effects in neurodegenerative disorders. According to the available literature on AMPK for AD, activation of AMPK is beneficial in autophagy, insulin resistance, mitochondrial quality control, and oxidative stress relief. It had been demonstrated that AMPK might become a novel target for AD by treating the risk factors [53]. According to a study, by decreasing oxidative stress and inflammation, DMB can be used as an AMPK stimulator to treat non-alcoholic fatty liver disease and to prevent the pathologic progression of non-alcoholic fatty liver disease to non-alcoholic steatohepatitis [34]. Thus, this shows that DMB may exert neuroprotective effects in AD by acute

activation of AMPK signalling, leading to downregulation of neuroinflammation and oxidative stress.

Demethyleneberbernine in Parkinson's disease

PD is a neurodegenerative condition distinguished by tenacious and selective loss of dopaminergic nerve cells in the substantia nigra, which add to the disease's cardinal motor symptoms: resting tremor, stiffness, and bradykinesia, along with dopaminergic neuropathology, cholinergic, serotonergic, glutamatergic, and nor-adrenergic pathways are malfunctioning [54]. Additionally, individuals with Parkinson's disease exhibit non-motor symptoms such as sleep problems, tiredness, and cognitive abnormalities. PD is a diverse disease that can proceed fast or slowly [55]. Pharmacologic treatments usually with levodopa formulations provided with or without other drugs and non-pharmacological methods, i.e., exercise, physical, occupational, and speech therapies, are utilized to treat the condition. Patients with drug-resistant tremors, dyskinesias, and worsening symptoms as the medicine wear off may benefit from treatment with levodopa-carbidopa enteral suspension and other approaches such as deep brain stimulation [56]. Since, berberine enhanced motor balance as well as coordination in PD by preventing dopaminergic neuronal loss in mice [9], indicating the possibility of the same effect by DMB. Among the numerous factors affecting the prognosis of PD, the importance of PI3K/AKT and p38 MAPK signalling in PD brains is captious because an imbalance between anti-apoptotic and pro-apoptotic pathways results in undesirable constellations such as microglial activation, oxidative stress, neuroinflammation, and apoptosis [57]. In the A53T model of α-synuclein, downregulation of p38 MAPK or overexpressing its kinase death variant lowers DRP1-mediated mitochondrial fission and restores mitochondrial dysfunction and cell death. Inhibiting the p38 MAPK-DRP1 signalling might be an essential therapeutic method for Parkinson's disease that maintains mitochondrial homeostasis [58]. As many studies revealed that DMB inhibits MAPK signalling [35], it can be further explored that DMB may serve a neuroprotective function in reducing PD symptoms via suppressing MAPK signalling. NF-κB, a well-characterized pro-death signalling pathway in response to oxidative stress, appears to be involved in the death of dopaminergic nerve cells in PD models [59]. The increased levels of NF-κB, interferon, and p53 in PD patients' nigrostriatal dopaminergic areas suggest an increase in immunological reactivity and programmed cell death of nerve cells [24]. NBD peptide enters the CNS in the MPTP model of Parkinson's disease, inhibits NF-κB signalling activation in the SNpc, and proinflammatory molecules' expression, glial cell activation in the midbrain, protects against dopaminergic neuron loss, and improves behavioural functions [60]. Since DMB is involved in the suppression of NF-κB [29], it can be supposed that DMB could be utilized to treat Parkinson's disease as a neuroprotective drug. AMPK regulates various physiological systems which can provide neuroprotection in PD, including energy balance, macro-autophagy, inflammation, antioxidant defences, and mitochondrial quality control. The degradation of particularly DA neurons and the subsequent motor-behavioural deficits associated with PD can be mimicked in experimental systems by administering dopaminergic poisons or expressing PD-related genetic abnormalities [61]. Since DMB promotes AMPK signalling [34], it may contribute to neuroprotection in PD via modulating AMPK signalling. Inhibitors of MAO-B are used to ameliorate symptoms of PD because they boost the level of synaptic dopamine by preventing the breakdown of the same. MAO-B inhibitors have a well-established role in Parkinson's disease patients as monotherapy or as adjuncts to levodopa. They are highly tolerated and uncomplicated to administer, making them ideal to commence therapy in eligible individuals [62]. DMB reversibly inhibited the MAO-B enzyme activity [63]; it has been hypothesized that DMB could be used to ameliorate PD symptoms.

Demethyleneberberine in Huntington's disease (HD)

HD is distinguished by motor, cognitive and behavioural manifestations. It occurs due to the expansion of a trinucleotide repeat on chromosome 4, specifically in the huntingtin gene (HTT) [64]. Although motor signs are currently used to define disease onset clinically, the presence of non-motor symptoms before motor diagnosis is becoming increasingly recognized. Complex multi-modal indications have a harmful effect on a patient's quality of life and longevity. Interdisciplinary symptomatic care delivered thoughtfully can have a significant positive impact on patients and families [65]. There are currently a variety of symptomatic treatments available, and new symptomatic and potentially disease-modifying therapies are being developed aggressively. HD is an appealing model for developing therapies capable of delaying or even halting the progression of neurodegenerative diseases. Tetrabenazine and deutetrabenazine are the only treatment options for this patient population with a formal indication (chorea) [66]. Berberine has also shown therapeutic potential in the transgenic mice model of HD [10] which means DMB might also have the same effect in HD as it is a metabolite of BBR. In numerous HD models, stimulation of the p38 MAPK and JNK pathways results in neural toxicity. In a 3-NP-treated HD mouse model, Rg1 was found to exert neuroprotective effects by suppressing the activation of MAPK and NF-κB signalling pathways in the striatum [67]. Since multiple studies have established DMB to be a MAPK signalling inhibitor [35], it can be

assumed that DMB may act as a neuroprotective agent in HD. In the striatum, the NF-κB cascade is activated in a variety of HD models. Studies in rodent models suggest a strong connection between neurodegeneration and NF-κB. 3NP induces nuclear translocation of NF-κB as well as nNOS and iNOS expression in Huntington's Disease, and that inhibition of NF-κB transcriptional activity blocks 3NP-induced NOS expression [67]. Since DMB inhibits NF-κB signalling [29], it may prove to be a neuroprotective agent by inhibiting NF-kB signalling. In cell and animal models of HD, the initiation of autophagy has been proven to be therapeutic. However, inducing autophagy through its primary regulator, i.e., mTOR, may have unintended consequences. According to a study, AMPK was recognized as a target for "mTOR-independent autophagy" enhancement in HD [68]. Since DMB activates AMPK signalling [34], which further initiates autophagy, it has given an idea of DMB's neuroprotective effect in HD by inducing autophagy.

Demethyleneberberine in amyotrophic lateral sclerosis (ALS)

ALS typically manifests in adulthood and is distincted by the selective death of cortical motor, bulbar and spinal nerve cells, resulting in early death and progressive paralysis, typically occurring some years after diagnosis. It is almost always fatal within a few years of symptom onset [69]. Besides riluzole supportive care, a putative glutamate release inhibitor is associated with modestly prolonged survival [70]. In the cellular model of ALS, berberine deregulated the mTOR/p70S6K signal and activation in the autophagic degradation pathway [43], suggesting the therapeutic potential of BBR in NDDs.Numerous MAPK inhibitors have also been assessed in pre-clinical and clinical studies for NDDs treatment. Despite encouraging results in some preclinical models, the MAPK pathway is essential for proliferation and cell survival, proliferation is a major concern. Several tested inhibitors of the MAPK pathway have significant side effects but this does not preclude MAPK members from being therapeutic targets, as several of these members exhibit cell-specific expression [71]. Since DMB inhibits MAPK [35], it may be used to slow the progression of Amyotrophic lateral sclerosis. In mice models, the novel molecular mechanism underlying motor neuron death in ALS is the downregulation of NF-κB activation in microglia with IGF-1 [72]. As DMB inhibits NF-κB signalling [29] so it can be used as a neuroprotective agent in ALS. The continuous activation of AMPK can be harmful in ALS to extremely stressed neurons. Thence, pre-conditioning with AMPK activating molecules can serve as a novel strategy for developing ALS. The latrepirdine preconditioning can delay the progression of ALS in $SOD1^{G93A}$ mice via activating AMPK signalling [34]. Since DMB is involved in activating AMPK signalling, it can be said that DMB may provide neuroprotection in ALS via acute activation of AMPK [73].

Demethyleneberberine in stroke

Stroke is ranked third as the cause of disability & death across the globe; it is undergoing a paradigm shift due to the disclosure of new concepts related to neurodegeneration [74]. Stroke as a blood vessel problem has been enlarged to incorporate the adverse consequences of an interaction involving neurons, glia, matrix components, and vascular cells. Secondary neuroinflammation occurs after an acute stroke, and most strokes are ischemic, which elevates additional injury and supports recovery [31]. The penetration of inflammatory cells, i.e., macrophages, neutrophils, countless T cell subtypes, and others into the ischemic region, aggravating brain injury is influenced by rapid activation of the resident cells by the pro-inflammatory signals from immune mediators [74]. The treatment of berberine ameliorated apoptosis induced by ischemia, and inhibited reactive astrogliosis and microglial activation in the gerbils model [44], suggesting the possibility of DMB having the same effect. IVIg therapy downregulated the MAPK and NF-κB signalling, consequently suppressing the activation & NLRP1 of the NLRP3 inflammasome in the primary cortical nerve cells during an ischemic episode. As a result of these findings, treatments that precisely target inflammasome activation in nerve cells may pave the way for future stroke treatment [75]. The use of a non-invasive molecular imaging technique in regulating the p38 MAPK signalling pathway can modulate MMP activity following stroke, elucidating a new mechanism of post-ischemic brain injury and circumventing the limitations of conventional MMP inhibitor therapy [76]. In a mouse stroke model, UTI guarded the brain in an ischemic episode due to its ability to alleviate inflammation in the early stages of the disease by downregulating TLR4 & NF-κB signalling expression [77]. DMB has been demonstrated to suppress NF-κB and MAPK signalling, implying that it may also act as a neuroprotective agent in stroke. Apelin 13 protected ischemia reperfusion-induced ROS mediated inflammation and oxidative stress in vivo by activating the AMPK/GSK-3 and AR/G/PLC/IP3/CaMKK signalling, further upregulating Nrf2-regulated antioxidant enzyme production [78]. As DMB activates AMPK signalling, it can be stated that its activation by DMB in stroke may play a significant role in alleviating stroke. This needs to be confirmed by further preclinical studies.

Demethyleneberberine in epilepsy

Epilepsy is frequently accompanied by various pathological and neurodegenerative changes in the brain regions

responsible for repetitive seizures. The changes include nerve cell loss and a rise in the size and number of astrocytes, additionally, they may also involve increased permeability of the blood–brain barrier, axonal sprouting, new capillaries, and central inflammation [79]. BBR has shown protection in various epilepsy models i.e., NMDA induced mice model, Kainic acid-induced mice model, Maximal electroshock mice model, and PTZ mice model [45], indicating the possibility of DMB having the same effect. Seizures trigger central nervous system inflammation, and NF-κB, chemokines, cytokines, cell adhesion molecules, and inflammatory molecules are expressed in the rodent brain [80]. Ghrelin decreases inflammation in cortical neurons during an epileptic seizure, which may help prevent necrosis and nerve cell death, preserving the cortex's normal function. Ghrelin may ease the cortex's inflammatory response by regulating TNF-α and NF-κB levels, reducing child epilepsy attacks frequently. These findings suggest that DMB can attenuate neuroinflammation in epilepsy via inhibiting NF-κB. AMPK has a role in epileptic seizures; for instance, time-restricted feeding increased AMPK phosphorylation and had an anticonvulsant effect in the model of status epilepticus. It was also observed that in the brain of acute and chronic seizures animals, the AMPK expression was decreased [81]. DMB activates AMPK [34]; DMB can show an anticonvulsant effect in epilepsy via activation of AMPK. SB203580 treatment significantly lowered the Racine scores and length of the initial seizure in rats. This result is the same as another study, which demonstrated that SB203580 considerably lowered the intensity and duration of seizures in a rat model of refractory epilepsy [82–84]. As DMB inhibits MAPK [35], it can be said that DMB can reduce the intensity of seizures via modulating MAPK signalling.

Conclusion

Innumerable medications have been used in the past to treat NDDs, but they lack the efficacy necessary to slow disease progression and instead create a host of harmful effects. In this light, plant-based medications have also evolved as a form of innovation. The diverse range of natural alkaloids continues to treat a variety NDDs effectively. We have discussed the neuroprotective properties of DMB, in a variety of neurodegenerative diseases in this review. Since DMB has been demonstrated to influence NF-κB, MAPK, and AMPK signalling in various disorders, it is evident that modulating these signalling pathways is crucial in NDDs. Thus, in this review, various ideas for future directions have been provided via correlating DMB and its modulation by NF-κB, MAPK, and AMPK signalling. As a result, DMB could show neuroprotective effects in various NDDS. There is very little availability of studies demonstrating DMB's role in NDDs. More scientific studies should be done in future to explore and evaluate the therapeutic potential of DMB in NDDs.

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