Palestinian Medical and Pharmaceutical Journal

Repurposing of Omeprazole in Neuroinflammation and Its Future Perspectives

Vrushali Neve[1], Kartik Panbhare[1], Pawan Karwa[1,*] & Deepali Kumari[2]

(Type: Review Article), Received: 8th May. 2024, Accepted: 2nd Sep. 2024, Published: 1st June 2025
DOI: https://doi.org/10.59049/2790-0231.10.2.2310

Abstract: Neuroinflammation is a complicated process that involves activating the brain's innate immune system in response to various stressors such as infection, injury, and neurodegeneration. The present review mainly focused on the possible signaling pathways and future potential targets for Omeprazole (OM) in neuroinflammation to combat neurodegenerative diseases like Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), stroke, traumatic brain injury (TBI) and many more.OM dramatically reduced TNF-α, IL-1β, and IL-6 levels. It also reduces oxidative stress by increasing the activity of antioxidants such as SOD, catalase activity, and palliating pro-oxidant malondialdehyde (MDA).OM suppressed inflammatory biomarkers by interrupting the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κβ) signaling pathway in gastrointestinal disorders and renal injury. Excessive NMDA receptor activation causes an influx of Ca^{2+} ions into the neuron, disrupting cellular homeostasis and producing reactive oxygen species. OM causes deregulation and injures mitochondrial-mediated ROS generation. OM potently diminished the malondialdehyde level, serum IL-1β and sE-selectin, and caspase-3, and increased levels of glutathione, Bcl-2 by PPAR-γ, NF-κB, and Nrf2/HO-1 Signalling Pathways.

Keywords: Omeprazole, Neuroinflammation, Reactive oxygen species, Interleukin, TNF receptor, nuclear factor kappa β

Introduction

Omeprazole (OM) was discovered by a team of scientists led by Drs. James W. Black, Robert A. Cobbin, and John S. Ford at Astra AB (AstraZeneca) in the late 1970s [1]. OM belongs to the type of drugs called proton pump inhibitors (PPIs) and exerts its therapeutic actions by irreversibly obstructing the H+/K+-ATPase enzyme on the secretory surface of gastric parietal cells [2]. It has IUPAC named as 5-methoxy-2-[(RS)-[(4-methoxy-3, 5-dimethylpyridin-2-yl) methyl] sulfinyl]-1H-benzimidazole [3]. It has a chiral center at the C-5 position of the imidazole ring and is chemically composed of a benzimidazole structure with a sulfinyl moiety. The S and R enantiomers are mixed in a racemic mixture, the drug's S-enantiomer being its active component. Its molecular weight is 345.42 g/mol with the chemical formula C17H19N3O3S (see Fig.1).

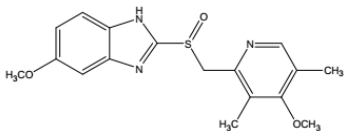

Figure (1): Chemical structure of Omeprazole.

Since its inception, OM has completely changed how acid-related conditions including gastroesophageal reflux disease (GERD) [4-6], peptic ulcers [7-9], and Zollinger-Ellison syndrome [10], and for the eradication of Helicobacter pylori infection [11, 12]. Despite this, many scientists are using OM in in-vitro and in-vivo models of neurodegenerative diseases including Parkinson's disease, traumatic brain injury, and neuropathic pain [13-17]. However, the exact mechanism by which OM exerted anti-neurotoxic action is still unknown. A Plethora of studies has suggested the anti-oxidative, anti-apoptotic, anti-secretary, autophagy inducer, and anti-inflammatory properties of OM in gastrointestinal, and kidney diseases [18-22]. So, in neuroinflammation, the above-mentioned beneficial effects of OM have not been illustrated yet. In this review, we will suggest the possible signaling pathways and future potential targets for OM in neuroinflammation to combat neurodegenerative diseases like Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), stroke, traumatic brain injury (TBI) and many more (see Fig.2).

1 Department of Pharmacology, Dr. D.Y. Patil Institute of Pharmaceutical Sciences and Research, Pimpri, Pune, Maharashtra, India.
*Corresponding author email: pawan.karwa@dypvp.edu.in
2 Department of Pharmacology and Toxicology NIPER Rabeareli, India.

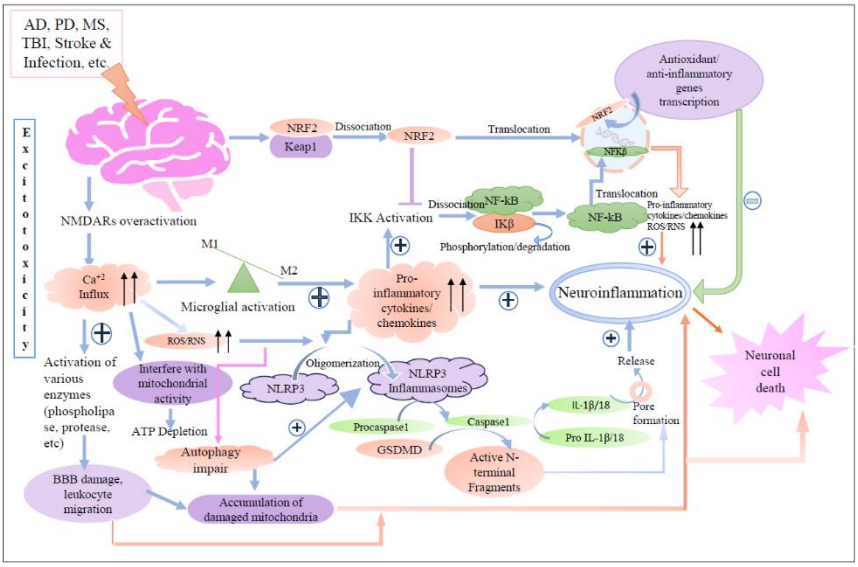

Figure (2): Schematic representation of different signaling activities leads to neuroinflammation in various brain disorders.

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Neuroinflammation is a complicated process involving activating the brain's innate immune system in response to various stressors such as infection, injury, and neurodegeneration [23]. This activation produces inflammatory mediators such as cytokines, chemokines, and reactive oxygen species (ROS), which can harm neurons and other brain cells [24]. Many research studies linked neuroinflammation with distinct neurodegenerative diseases such as AD [25, 26], PD [27, 28], MS [29, 30], stroke [31, 32], TBI [33, 34], epilepsy [35, 36], and certain psychiatric disorders like depression [37, 38] and schizophrenia [39, 40]. The immune response and inflammatory processes within the central nervous system (CNS) can cause damage to neurons, alter normal brain functioning, and contribute to illness progression in several conditions. However, limited drug therapies are available for neuroinflammatory diseases in the market, to combat the scenario the well-known PPI inhibitor OM can be beneficial approach towards neuroinflammation. The precise methods by which omeprazole exerts its putative anti-inflammatory benefits in neuroinflammation are unknown. In this review we will suggest several possible ways by which OM may alter neuroinflammation (see Fig 3)

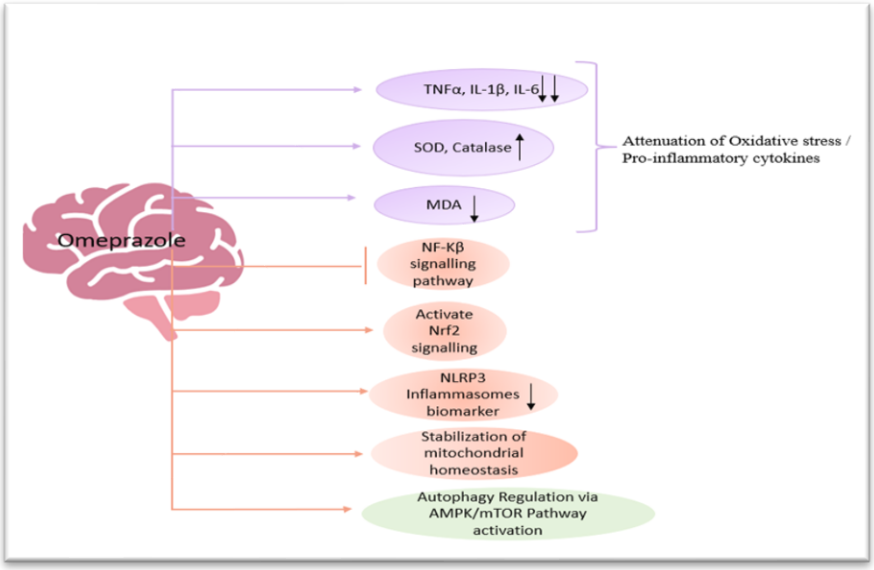

Figure (3): The potential effect of Omeprazole against the various biomarkers of neurodegenerative disorders.

Role of microglial activation in neuroinflammation

Microglias, which are resident immune cells in the CNS responsible for immunological monitoring and defense, are a major factor in neuroinflammation. Microglia can be activated by a variety of cues, including injury, infection, or inflammatory biomarkers generated by injured cells [41- 42]. Changes in morphology, gene expression, and functional features accompany the transition from a resting to an activated state. It activation can be divided into two categories: proinflammatory (M1) and anti-inflammatory (M2) [42, 43].

Proinflammatory microglia (M1) releases a variety of chemicals that contribute to the inflammatory response in neuroinflammation. These include proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6) interleukin-18 (IL-18) [44, 45]. These cytokines can recruit immune cells, activate astrocytes, and contribute to the blood-brain barrier breakdown [46]. Furthermore, proinflammatory microglia emit reactive oxygen species (ROS), nitric oxide (NO), and other toxic biochemicals that can cause neuronal damage and neurotoxicity [47, 48].

They also express surface receptors such as toll-like receptors (TLRs), which recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), increasing the inflammatory response even

more [49, 50]. On the other hand, anti-inflammatory microglias (M2) are engaged in the resolution of neuroinflammation and tissue restoration. They release anti-inflammatory cytokines like interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), which can inhibit proinflammatory cell activation and dampen the inflammatory response, as shown in figure 1 [51, 52]. M2 microglia are further distinguished by their phagocytic solid activity and neurotrophic factor release, including the brain-derived neurotrophic factor (BDNF) [44], and also the insulin-like growth factor-1 (IGF-1) [53], and the nerve growth factor (NGF) [42]. These substances boost neuronal survival, synaptic plasticity, and tissue repair. A range of variables in the CNS microenvironment dynamically influence microglia polarization. Signals from neurons, astrocytes, and invading immune cells can all impact microglia. Astrocytes, a glial cell in the CNS typically A2 polarized, can release soluble molecules that induce M2 polarization and reduce microglia's proinflammatory response [54].

The M1 and M2 microglia balance is critical for immunological homeostasis in the CNS. Neuroinflammation can develop when the balance shifts toward M1 microglia which ultimately leads to neuronal damage and neurodegenerative diseases, such as Alzheimer's disease [55] and Parkinson's disease [56], stroke [57], multiple sclerosis [58], and many more. Sadayuki Hashioka and their co-workers found the anti-neuroinflammatory property of OM on the toxic action towards SH-SY5Y neuroblastoma cells of supernatants from human microglia and THP-1 cells stimulated by lipopolysaccharide (LPS) combined with interferon-γ [15]. This effect is produced upon decreasing the secretion of TNF-α and IL-6 from the stimulated THP-1 cells which are in concentration-dependent manner [15].

Consistently, Hashioka et al. (2011) established the cytoprotective, anti-neurotoxic, and anti-neuroinflammatory activities of OM by attenuating interferon-γ triggers signal transducer and acts as a activator for transcription 3 (STAT3) phosphorylation, which produced neurotoxicity to human glial U-373 MG cells or U-118 MG cells at a 10 µM concentration [13]. According to Chanchal et al., 2016, have indicated that OM ameliorates the neuropathic pain in adult male Wistar rats at a dose of 50mg/kg/day/oral for 14days stimulated by chronic constriction injury (CCI) model [17]. ROS generation in U-87 cells induced by LPS induces inflammation in-vitro. Compared to their control groups, OM dramatically reduced TNF-α, IL-1β, and IL-6 levels. It also reduces oxidative stress by increasing the activity of antioxidants such as SOD, catalase activity, and palliating pro-oxidant malondialdehyde (MDA). Similarly, in-vitro study, OM reduced the oxidative stress as well as the release of TNF-α, IL-1β, and IL-6 in LPS-mediated ROS-induced U-87 cells [17]. Although the precise signaling pathway by which OM shows neuroprotective actions is not clearly known. More research is required to discover the crystal-clear mechanism of OM in neuroinflammatory-linked neurological disorders.

Role of NF-κβ pathway in neuroinflammation

From the distinct review of the literature, it was found that OM suppressed inflammatory biomarkers by sowing intruptions in the nuclear factor kappa-light-chain-enhancer which iniciated the B cells (NF-κβ) signaling pathway in gastrointestinal disorders and renal injury [18, 59-63]. NF-κβ is a transcription factor, that regulates the immunological and inflammatory responses, including neuroinflammation [64, 65]. It plays a crucial role in modulating inflammation, immune response, cell survival, and apoptosis-related gene expression. The NF-κβ signaling pathway can be activated by various stimuli, including pro-inflammatory cytokines, such as TNF-α [66] and IL-1β [67, 68], PAMPs, such as LPS from bacteria [50], and DAMPs, like ATP released from damaged cells [69], oxidative stress, and other cellular stressors. The activation of NF-κβ involves a complex series of events, including receptor stimulation, IκB degradation, nuclear translocation, and finally production of inflammatory cytokines.

The signaling cascade is initiated by the binding of ligands, such as TNF-α or IL-1β, to their corresponding cell surface receptors. These ligands binds to cell surface tumor necrosis factor receptors (TNFR) and also to the interleukin-1 receptors (IL-1R) [50]. Following ligand binding, it activates a multiprotein complex known as Iκβ kinase (IKK) complex. The IKK complex consists of two catalytic subunits, IKKα and [67] IKKβ, and a regulatory subunit called IKKγ (also known as NEMO) as shown in (see fig 4).

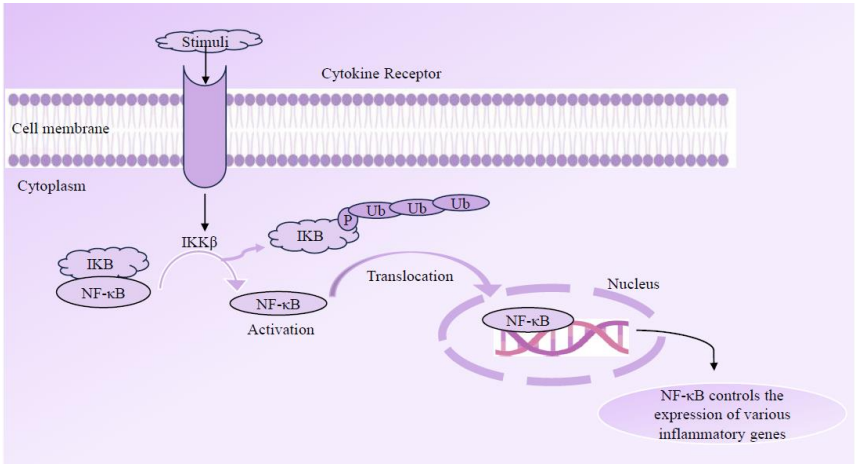

Figure (4): NF-κB activation pathway leads to phosphorylation of IκB by IKKβ to its ubiquitination and subsequent proteasomal degradation of IκB, the active form of NF-κB is released and translocates into the nucleus. This translocation allows NF-κB to bind to specific DNA sequences known as κB sites in the promoter regions of target genes and generates inflammatory biomarkers.

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Depending on the stimuli and cell type, the specific amino acid residues involved in NF-κβ activation can vary. However, the serine residues (Ser32 and Ser36) in the IκBα protein are a crucial location for NF-κβ activation [68, 70]. Phosphorylation of IκB by IKKβ leads to its ubiquitination and subsequent proteasomal degradation. This degradation releases the sequestered NF-κB dimers (typically composed of p50 and p65 subunits) from the cytoplasmic complex and allows them to translocate into the nucleus. This translocation allows NF-κB to bind to specific DNA sequences known as κB sites in the

promoter regions of target genes. These genes encode various pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6), chemokines (e.g., MCP-1), adhesion molecules, and other inflammatory mediators that help recruit immune cells to the site of inflammation and amplify neuroinflammation. Overproduction of pro-inflammatory cytokines and ROS can induce neurotoxicity, disrupt synaptic function, and promote neuronal death. Several studies have shown the detrimental effect of NF-κβ-mediated neuroinflammation in neurodegenerative diseases likes, AD [64] PD [65], stroke [57], and MS [71].

Sustained or severe NF-κβ activation, on the other hand, might result in chronic inflammation and neuronal injury. Furthermore, NF-κβ activation can increase the production of pro-apoptotic genes, which contributes to neuronal apoptosis [72, 73] It has been already established that NF-κβ inhibition by OM in gastrointestinal diseases [59-62]. However, the neuroprotective role of OM has not been clearly elucidated yet against NF-κβ. Rabab Shaban El-shafey and co-workers have investigated the antioxidative, anti-apoptotic, and anti-inflammatory effects of wheat germ oil (WGO), and OM as standard in ethanol-triggers gastric mucosal injury in adult albino rats. In this study, OM potently suppressed pro-oxidants including MDA and nitric oxide while increasing antioxidants like Nrf2, and HO-1 gene expression, and improving serum GSH, and catalase. Despite this, OM group significantly increased serum anti-inflammatory biomarkers such as IL-10 and severely dampened pro-inflammatory cytokines like TNF-α and IL-1β.

Immunohistochemical findings of their study have shown that this effect produced by markedly decreased in expression of NF-κB-mediated inflammation [59]. Likewise, Badr et al., 2019, have published a research work and revealed the mechanism of pre-treated Raspberry Ketone (RK) (50 mg/kg) orally and OM (20mg/kg) against ethanol-induced gastric ulcer in adult male Wistar rats [60]. RK and OM significantly attenuated gastric injury by elevating antioxidants protein expression of Nrf2 and suppressed proinflammatory biomarkers such as HMGB1 which is measured by western blot and NOX-1/2, NOX-4, TNF-α, and NF-κB estimated by using ELISA technique [60]. Raishet al., 2018, has found the effect of polysaccharides from *M. charantia* (MCP) (300 mg/kg p.o.) and OM in Wistar rats against the ethanol-stimulated gastritis by activation of the NF-κB signaling pathway [61]. MCP and OM groups repressed the gastric inflammation via depleting of MPO, TNF-α, and IL-6 secretions and prohibited oxidative stress by diminishing lipid peroxidation along with the noteworthy increment in glutathione and catalase activity.

In addition to this, the apoptotic biomarkers Bax and caspase-3 suppressed and enhanced the anti-apoptotic protein Bcl-2, which promotes cell survival [61]. In this review article, we suggest the anti-neuroinflammatory effect of OM could be mediated through the inhibition of NF-κB signaling pathways.

Role of NMDA receptors in neuroinflammation and mechanism of omeprazole to decrease NMDA receptors activation

N-Methyl-D-Aspartate (NMDA) receptors are an ionotropic glutamate receptor subtype that plays a critical role in synaptic plasticity, learning, and memory formation and excitatory neurotransmission in the encephalon [74 -75].

They are named after the synthetic compound NMDA, which selectively activates these receptors. The NMDA receptors consists of multiple subunits, which specifically contains the two GluN1 subunits and two GluN2 subunits [75, 76]. The GluN1 subunit is required for receptor function and can produce receptor subtypes with varied features when combined with different GluN2 subunits. NMDA receptor subtypes include GluN2A, GluN2B, GluN2C, and GluN2D, which are broadly dispersed throughout the brain. The interaction of glutamate, a key excitatory neurotransmitter, and the co-agonist glycine or D-serine is required for NMDA receptor activation. NMDA receptors are distinguished by their voltage-dependent activation, which means that channel opening requires the simultaneous fulfilment of two conditions: presynaptic depolarization and the removal of a magnesium (Mg^{2+}) ion block from the receptor's pore [77, 78].

As a result, NMDA receptors are very sensitive to synaptic activity patterns and the overlap of pre- and postsynaptic firing. When the NMDA receptor channel opens, cations, including calcium (Ca^{2+}), can enter the postsynaptic neuron. Calcium is essential for several cellular functions and signaling pathways in the CNS. However, overactivation of NMDA receptors, which results in an excessive calcium influx, can set off a chain of events that can result in Ca^{2+} toxicity or excitotoxicity, superoxide generation, and neuroinflammation in many neurological illnesses, as shown in figure 3 [79-81]. The role of NMDA activation in neuroinflammation is complex and multifaceted [82, 83]. The therapeutic use of OM against NMDA receptors has not been studied yet in neuroinflammatory diseases. A study done by Cerbo et al. has depicted the protective effect of aqueous extract of Borago officinalis L. and OM on physical (stress)-induced gastric ulcers in a rat model by modulation of the NR2A and NR2B subunit expression [84].

In addition, excessive Ca^{2+} influx overwhelms the cell's calcium buffering capacity, resulting in an overload of intracellular Ca^{2+}. The elevated Ca^{2+} levels activate various enzymes, including phospholipases, proteases, and nitric oxide synthase [85-87].A study by Kamiya et al., 2021 demonstrated that OM dose-dependently (10–1000 μM) attenuated bradykinin (BK) and thapsigargin-induced endothelial Ca^{2+} action [88]. OM repressed Ca^{2+}drives phosphorylation of endothelial nitric oxide synthase (eNOS) at Ser1177 leading to diminished BK and thapsigargin triggering nitric acid formation [88].Excess Ca^{2+} in the cytosol can interfere with mitochondrial activity. Mitochondria are critical components of cellular energy production and calcium homeostasis.

Disruption of mitochondrial function can result in ATP depletion, the generation of ROS, and the release of pro-apoptotic proteins, all of which contribute to cell death, as shown in figure 3 [88, 89]. These processes can damage cellular components and initiate inflammatory responses [90, 91]. The results of a study by Gao et al., 2018 have indicated that OM at a concentration of 40 μg/mL significantly reversed the mitochondrial morphology, deregulation, and injured mitochondrial-mediated ROS generation in cisplatin-induced renal failure in in-vivo SD rats and in-vitro by using human renal tubular HK-2 cells [63].

In addition to this, they also revealed that OM exerted a renoprotective effect by diminishing apoptosis and NF-κB derived inflammation [63].Gislaine T. Rezin and his research investigated the antioxidative effect of the combination of OM with N-acetylcysteine (NAC) and the gastrin-releasing peptide receptor (GRPR) antagonist RC-3095 against indomethacin (IDM)-induced gastritis. There results showed that OM and RC-3095 drugs reversed IDM-mediated inhibition of mitochondrial respiratory complex III and prevents ATP depletion and ROS generation[92].

This possible effect of OM on mitochondrial deregulation in neuroinflammatory link diseases, however, has yet to be investigated. In this review, we suggest that OM can be repurposed for neuroinflammation by exploiting this mechanism. NMDA receptor activation can cause activated microglia and astrocytes to release pro-inflammatory cytokines such as IL-1β,

TNF-α, and IL-6 [93-95]. Following activation, this results in their morphological and functional changes, as well as the activation of more immune cells and the creation of inflammatory mediators [96, 97]. More research is needed to determine the precise mechanism of OM action on NMDA receptors in neuroinflammation. We propose that OM may suppress MMDA-mediated neurotoxicity by lowering proinflammatory biomarker release from astrocytes and microglia, as well as ROS formation, although more in-vitro and in-vivo research is needed to validate its function in neuroinflammation. This could be a game changer in terms of repurposing OM use against neuroinflammation.

2.4 Role of Reactive Oxygen Species in neuroinflammation:

Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the ability of cells to detoxify or repair the resulting damage [98]. ROS are highly reactive molecules that contain oxygen atoms and can be generated during normal cellular metabolism as well as through exposure to external sources. It leads to many pathological conditions and is related to numerous diseases, including cardiovascular diseases [99, 100], cancer [101, 102], pulmonary diseases [103, 104], neurodegenerative disorders [105, 106].

It is generated during various metabolic events within cells by the incomplete reduction of molecular oxygen (O2). The electron transport chain (ETC) is a primary source of ROS generation in mitochondria. Electrons are transferred along a sequence of protein complexes in the inner mitochondrial membrane during oxidative phosphorylation. Some electrons may leak prematurely from the ETC, resulting in the generation of superoxide (O2•), the main ROS [107]. Within the ETC, the primary locations of electron leakage are complex I and complex III. Enzymatic reactions involving NADPH oxidase and nitric oxide synthase (NOS) can also generate ROS [108]. Superoxide anion is relatively unstable and can dismutate spontaneously or enzymatically to form hydrogen peroxide (H2O2). The hydroxyl radical (OH•) is one of the most reactive ROS and is generated via the Fenton reaction, which occurs when H2O2 reacts with metal ions (such as iron or copper) [109, 110]. The hydroxyl radical can cause severe damage to DNA, proteins, lipids, and other cellular components [111, 112].

Despite this, nitric oxide is a signaling molecule that is involved in a variety of physiological activities. Under some conditions, however, nitric oxide can react with superoxide anion to generate peroxynitrite (ONOO-), a highly reactive oxidant capable of causing oxidative damage to proteins, lipids, and DNA [113, 114]. The body contains a comprehensive antioxidant defense system that comprises unique enzymes to fight the detrimental effects of ROS. SOD catalyzes the conversion of superoxide radicals (O2-) into H2O2 and molecular oxygen (O2) [115]. SOD is found in three separate cellular compartments: copper-zinc SOD (CuZnSOD), manganese SOD (MnSOD), and extracellular SOD (EC-SOD). SODs are thought to be the initial line of defense against ROS. Catalase is mostly present in peroxisomes and is in charge of breaking down H2O2 into water (H2O) and molecular oxygen (O2). It aids in the prevention of H2O2 build-up, which can be damaging to cells if not effectively removed. Glutathione peroxidase (GPx) is an enzyme family that uses glutathione (GSH) as a co-substrate to convert H2O2 or lipid hydroperoxides into water or equivalent alcohols [116]. GPx enzymes perform a crucial role in protecting cells from oxidative damage, especially in eliminating peroxides from lipid membranes. Glutathione reductase (GR) converts oxidized glutathione disulfide (GSSG) into reduced glutathione (GSH) [117].

GSH is a powerful antioxidant, either directly scavenging free radicals or helping in the regeneration of other antioxidants like vitamin C and vitamin E. Accumulating shreds of evidence indicated that ROS has an impact on neuroinflammation in various ways studied in neurological diseases including AD [24, 118], PD [119, 120], MS [121, 122], HD [123], stroke [124], TBI [125], and many more. ROS induces neuroinflammation by activating microglia which leads to polarization of microglia in M1 [126]. DAMPs are produced by activated microglia, which release pro-inflammatory cytokines, chemokines, and ROS. Excessive excitatory neurotransmitter release from neurons, such as glutamate, can result from oxidative stress.

This excess glutamate can over-stimulate glutamate receptors, especially NMDA receptors, resulting in a calcium ion influx into neurons [127]. Calcium overload sets off a chain of events that causes oxidative stress, aggravating inflammation and neuronal damage or death as discussed earlier. ROS produced under oxidative stress can cause DNA and protein damage in neural cells. DNA damage can activate DNA repair processes, which can then cause inflammation [120, 128].

Furthermore, damaged proteins can lose their normal function, aggregate in cells, and activate immunological responses, all of which contribute to neuroinflammation. Various signaling pathways implicated in inflammation, including as NF-κB and mitogen-activated protein kinases (MAPKs), can be activated by oxidative stress [129- 130]. These pathways control the generation of pro-inflammatory cytokines, chemokines, and adhesion molecules, which attract and activate immune cells at the site of inflammation. Increased production of these inflammatory mediators stimulates the brain's inflammatory response.

The well-known antioxidative and ani-inflammatory role of OM in gastro and renal related diseases has been already established [131][22]. Lu Xie and his colleagues discovered a synergistic gastroprotective effect of OM and Patchouli Alcohol (PA) extracted from Pogostemonis Herb a in in-vitro H2O2-triggers gastric epithelial cells (GES-1) and LPS-stimulated RAW264.7 cells, as well as in-vivo ethanol-induced gastric ulcer in male SD rats [131]. This combination has demonstrated antioxidant activity by decreasing lipid peroxidation and enhancing antioxidant machinery such as CAT, SOD, and GSH. In the setting of anti-inflammation, IL-6, IL-10, and TNF-α level evaluated using an ELISA kit in the OM and PA groups are significantly lower than in the illness group. In addition to anti-oxidative and anti-inflammatory properties, this combination increased Bcl-2 levels and decreased cleaved caspase 3 and BAX protein expressions, perhaps via interfering with the MAPK pathway [131]. Mohammed Z. Nasrullah and colleagues discovered that OM protects the kidneys from colistin-induced oxidative stress, apoptosis, and inflammation in male Wistar rats.

The OM mitigated oxidative stress by dampening MDA levels and surpassed antioxidant enzymes GSH, CAT, SOD, and proinflammatory cytokines IL-6 and TNF-α as measured by the ELISA technique. The results also demonstrated that OM reduced apoptosis by decreasing BAX mRNA expression and increasing Bcl-2 level [22]. In an 8-day research of isoproterenol (ISO) (150 mg/kg, s.c.) caused myocardial infarction in Wistar rats, Ashwini S. Patil, and co-scientist studied the antioxidative and anti-inflammatory effect of OM and Lansoprazole at 50 mg/kg/day, p.o, separately. The results showed that both PPI dramatically reduced pro-oxidants like MDA and NO while increasing endogenous antioxidants like CAT, SOD, and GSH as compared to the disease group. The PPI also lowered TNF-α levels and protected the heart against the detrimental effects of ISO [132]. Despite this, neuroprotective, antioxidative, and anti-

neuroinflammatory role of OM has not been studies yet. However, some accumulated reports suggested the dual role of OM in neurodegenerative diseases. On the one hand, OM potently inhibits oxidative stress and neuroinflammation but on the opposite site, it exhibits a pernicious effect [132- 133].

So, it needs tremendous attention towards in-vitro and in-vivo studies to repurpose OM in neuroinflammation-linked neurological disorders. Abo El and coworkers investigated the gastro and neuroprotective activities of adropin and OM in indomethacin (IND)-induced gastric ulcer in a rotenone-induced PD in male albino rat model. Both adropin and OM dramatically reduce the MDA level while significantly increas ing the level of endogenous antioxidants such as SOD and CAT in serum as measured by the colorimetric test. The OM and adropin groups had higher DA levels measured by ELISA, which were reduced by rotenone in the illness group; this effect is mostly due to regulation of the PI3K/AKt pathways[134].

The clinical study by Avraham Weiss and his research team hypothesized that the long-term use of OM in elders over the age of 65 reduced dementia/cognitive decline, possibly through lowering oxidative stress and neuroinflammation [135]. Asirvatham et al. revealed that the long-term usage of OM 20 mg/kg for 21 days caused neurobehavioral impairments in rats such as decreased locomotor activity, memory, and learning. OM also raises MDA levels while decreasing CAT, SOD, GSH, and neurotransmitters such as acetylcholine, dopamine, noradrenaline, and serotonin. In contrast, 400 mg/kg of Pluchea lanceolata hydroalcoholic extract (HAEPL) effectively reversed the aforesaid parameters and exerted neuroprotective benefits [136]. Similarly, Dries et al., 2020 found that prolonged use of OM in humans causes oxidative stress, which leads to cognition deficits and neurotoxicity [133]. To validate the exact role of OM in neuroinflammation needs more in-vitro and *in-vivo* studies.

Role of Nuclear factor erythroid 2-related factor 2 (Nrf2) neuroinflammation and mechanism of OM on Nrf2

Nrf2 is a key transcription factor crucial in cellular defense against oxidative stress and neuroinflammation [137-139]. It functions as a master regulator of antioxidant response elements (AREs) and regulates the expression of several cytoprotective genes. The activation of Nrf2 is a multifaceted process that includes both upstream and downstream effects. In canonical, under basal conditions, its negative regulator, Kelch-like ECH-associated protein 1 (Keap1), keeps Nrf2 in the cytoplasm. Keap1 is an adaptor for the Cullin3-based E3 ubiquitin ligase complex, which targets Nrf2 for proteasomal degradation, hence keeping a low level of Nrf2 in the cytoplasm [140- 141]. Oxidative stress, electrophilic chemicals, and ROS can all change key cysteine residues on Keap1.

This change breaks the Keap1-Nrf2 connection, preventing Nrf2 deterioration [142-144]. There is a non-canonical mechanism for Nrf2 activation in addition to the canonical pathway. Proteins such as p62, p21, and dipeptidyl peptidase III (DPP3) are involved in this process [145], and the Wilms tumor gene on X chromosome (WTX) can interact with Keap1 and disrupt the Nrf2-Keap1 complex [146]. Even without oxidative stress, Nrf2 can be released from Keap1 and activated. Nrf2 accumulates in the cytoplasm and translocates into the nucleus after being released by Keap1. This translocation is facilitated by importin-α/β proteins [147]. Nrf2 forms a heterodimer with a tiny Maf protein in the nucleus and binds to the ARE sequence, triggering the transcription of cytoprotective genes. Among these genes are heme oxygenase-1 (HO-1) [148], glutathione peroxidase (GPx) [149- 150], glutamate-cysteine ligase (GCL), and NADPH-quinone oxidoreductase 1 (NQO1) [151]. Stimulation of Nrf2 leads to elevating the expression of these genes, amplifying cellular antioxidant capacity.

By blocking the activation of pro-inflammatory transcription factors such as NF-κB, Nrf2 activation can decrease inflammation, mainly mitigating the expression of pro-inflammatory cytokines, chemokines, and adhesion molecules [152, 153]. Nrf2 has emerged as a crucial regulator in microglial activation and neuroinflammation. As discussed earlier, Microglia activation is linked to the release of pro-inflammatory cytokines, chemokines, reactive oxygen species (ROS), and other inflammatory mediators. The activation of Nrf2 in microglia has been demonstrated to have several positive benefits, including reducing the release of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 [154- 155]. This anti-inflammatory impact is done by upregulating the expression of Nrf2 target genes that encode anti-inflammatory proteins and downregulating NF-κB signaling, a crucial route in inflammatory reactions. (see Fig 5).

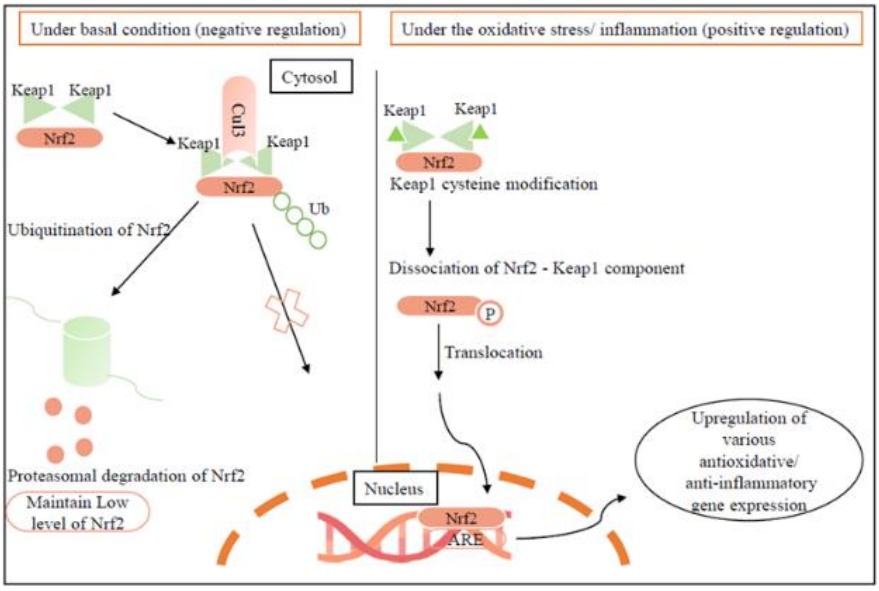

Figure (5): Nuclear factor erythroid 2-related factor 2 (Nrf2) neuroinflammation and mechanism of OM on Nrf2

*The above figure is original and was created by the authors specifically for this study.

Surprisingly, the Nrf2 and NF-κB signaling pathways interact and can influence each other's activity. Several studies have shown that Nrf2 can affect NF-κB signaling components in various ways: Nrf2 activation can reduce NF-κB signaling by suppressing IκB kinase (IKK) activation, which is responsible for the phosphorylation and degradation of IκB proteins. Nrf2 indirectly suppresses NF-κB translocation into the nucleus by limiting IκB breakdown, lowering the expression of NF-κB dependent genes [156-158].

Nrf2 can also influence the expression of NF-κB target genes. For example, Nrf2 activation has been found to suppress the expression of NF-κB regulated pro-inflammatory genes such as IL-6, IL-1β, and TNF-α [62, 159]. By reducing the expression of these pro-inflammatory factors, Nrf2 can attenuate the inflammatory response mediated by NF-κB. Ample in-vitro and in-vivo studies have proved the antioxidant, anti-inflammatory, and anti-apoptotic effects of OM via activation of Nrf2 in gastrointestinal and many more diseases [59, 60, 62, 153, 160, 161]. Becker et al. (2006) have suggested the cytoprotective antioxidative and anti-inflammatory effect of OM at a concentration of 300µM in human epithelial cells (KATO III and AGS) as well as rat epithelial cells (RGM) against oxidative stress.

OM has potently increased HO-1 levels in mRNA and western blots while decreasing cyclooxygenase, which attenuates oxidative stress and cell death [162]. Ananddeep Patel and colleagues demonstrated that OM, at a dosage of 100µM, mitigated cytotoxicity and H2O2 levels caused by DMSO in fetal human pulmonary microvascular endothelial cells (HPMEC), potentially through upregulating Nrf2 mRNA and protein levels [163]. Several scientists have established a strong link between Nrf2-mediated suppression of inflammatory biomarkers via interrupting NF-κB signaling.Mohammad Raish and his colleagues studied the cytoprotective, antioxidative, and anti-inflammatory effects of sinapic acid and OM as a standard against ethanol-stimulated gastric ulcers in male Wistar rats. SA and OM significantly lowered MDA by colorimetric assay, TNF-α, IL-6, myeloperoxidase (MPO) assessed using ELISA kit, caspase-3, Bax, and Bcl-2, and NF-κB (p65) detected by western blot. Simultaneously, it augmented the levels of antioxidative enzymes such as diminished glutathione (GSH) and catalase, as well as the expression of the Nrf2 protein [62].

Magdy Mahmoud-Awny and co-workers have investigated the antioxidative, anti-inflammatory, and anti-apoptotic effect of Mangi Ferin a xanthonoid obtained from Mangifera indica and OM taken as standard in ischemia/reperfusion rat model of gastric ulcer. In this study, both Mangi Ferin and OM potently diminished the malondialdehyde level, serum IL-1β and E-selectin, and caspase-3, and increased levels of glutathione, Bcl-2 by PPAR-γ, NF-κB, and Nrf2/HO-1 Signalling Pathways[164]. However, the anti-neuroinflammatory effect of OM through Nrf2/NF-κB signalling pathway has not been elucidated yet. We suggested in this review article, that this will be out of box use of OM in neuroinflammatory diseases.

Autophagy in neuroinflammation

Autophagy plays a vital role in removing aggregated or misfolded proteins, especially those linked with neuroinflammatory disorders like AD [165], PD [166], stroke [167], and HD [168]. It is double sword machinery has been demonstrated to have both protective and pathogenic consequences in the context of neuroinflammation, depending on the conditions.

Accumulation of these abnormal proteins can trigger inflammation and cellular stress responses, contributing to neuroinflammation [169, 170]. It also regulates immunological responses, including those in the brain. It can influence the activation and behaviour of immune cells like microglia and astrocytes, which are important participants in neuroinflammatory processes.

Autophagy activation can influence the immune response in neuroinflammation by promoting the clearance of cellular debris, aberrant and aggregated proteins, and regulating the release of pro-inflammatory cytokines. It is activated by a variety of signalling mechanisms, including nutritional deprivation [171], oxidative stress, and immune responses [172, 173]. The mechanism of autophagy activation involves several key steps:

Initiation: Autophagy is initiated by the formation of a double-membrane structure called the phagophore or isolation membrane. The mammalian target of rapamycin complex 1 (mTORC1) pathway is principally responsible for autophagy inhibition. When food supply is limited or during cellular stress, mTORC1 activity declines, resulting in autophagy activation [174, 175]. Furthermore, the adenosine monophosphate-activated protein kinase (AMPK) pathway has significance in autophagy. When cellular energy levels are low, such as during nutritional deprivation or low ATP levels, AMPK, a cellular energy sensor, is activated. AMPK activation phosphorylates and inhibits mTOR, facilitating autophagy initiation [176-178].

Nucleation: Several protein complexes are needed for phagophore formation, including the ULK1 (Unc-51-like kinase 1) complex, which consists of ULK1, FIP200, ATG13, and ATG101 [179, 180]. The ULK1 complex is triggered by AMPK phosphorylation of ULK1 and mTOR inhibition. When activated, the ULK1 complex recruits' other autophagy-related proteins to begin building autophagosome.

Elongation: The Beclin 1 protein forms a complex with the class III PI3K termed VPS34 (vacuolar protein sorting 34). This complex phosphorylates phosphatidylinositol lipids to produce phosphatidylinositol 3-phosphate (PI3P), an autophagosome formation regulator [181-183]. The Beclin 1-VPS34 complex interacts with other ATG proteins to form the pre-autophagosomal structure (PAS), which includes ATG14, VPS15, and ATG16L1.

These proteins aid in the transport and assembly of the lipid phosphatidylinositol 3-phosphate (PI3P) to the PAS. Once produced, the phagophore elongates and engulfs cytoplasmic cargo such as damaged organelles and protein aggregates. Two ubiquitin-like conjugation systems are involved in this process: the ATG12-ATG5-ATG16L1 complex and the microtubule-associated protein 1 light chain 3 (LC3)-phosphatidylethanolamine (PE) conjugation system[184]. The ATG12-ATG5-ATG16L1 complex conjugates ATG12 to ATG5, which then binds to ATG16L1 to form a complex that can be observed on the phagophore's outer membrane[185]. ATG4 cleaves LC3 to expose a C-terminal glycine residue attached to PE. The lipidated version of LC3, or LC3-II, is inserted into the developing autophagosome's inner and outer membranes.

Maturation: The autophagosome merges with lysosomes to produce an autolysosome, where lysosomal enzymes destroy the sequestered cargo[186]. Proteins such as soluble N-ethylmaleimide-sensitive factor attachment protein receptors (SNAREs) and Rab GTPases mediate this fusion. The breakdown products of the cargo are subsequently released into the cytoplasm for recycling and use by the cell. Recent research has focused on the interaction between autophagy and the NLRP3 inflammasome in neuroinflammation[187, 188].

Furthermore, specific signaling pathways and biochemicals are known to link autophagy and the NLRP3 inflammasome. AMPK, a master regulator of cellular energy metabolism can induce autophagy while inhibiting NLRP3 inflammasome activation [176, 189]. Recent research has focused on the interaction between autophagy and the NLRP3 inflammasome in neuroinflammation. Elevated autophagy can enhance the breakdown of NLRP3 inflammasome components, which may mitigate inflammation [190-192].

Impaired autophagy, on the other hand, can result in the buildup of damaged mitochondria and increased NLRP3 inflammasome activation, aggravating neuroinflammation[193, 194]. It has the ability to regulate the secretion of pro-inflammatory cytokines such as IL-1β, which is processed and produced when the NLRP3 inflammasome is activated. Several more investigations have revealed that autophagy preferentially sequesters and degrades IL-1β within autolysosomes, limiting its release and reducing the inflammatory response [189, 191, 192].

Currently, many researchers like Arab et al., 2021, [20], Arabet al., 2022, [178],and others have revealed the mechanism of OM by inhibiting either or both NLRP3 inflammasome-mediated inflammatory biomarkers and attenuating inflammation by inducing autophagy in in-vitro and in-vivo models [19, 195]. Hany H. Arab and coworkers researched the anti-inflammatory impact of saxagliptin (10 mg/kg) and OM (20 mg/kg) orally in ethanol-induced stomach mucosal damage in 6-8-week-old male albino Wistar rats. In this study, the results revealed that saxagliptin and OM groups markedly surpassed the expression of LC3-II and Beclin 1, whereas diminished autophagy repressor p-mTOR/mTOR signal possibly by activating AMPK pathway, as elevated in the ethanol group. Furthermore, these drugs significantly increased the expression of NLRP3, ASC, caspase-1, and nuclear NF-κBp65 measured by western blot, resulting in suppressed secretion of IL-1β determined by ELISA kit. Despite this, it dampens pro-oxidants and apoptotic biomarkers and, on the other hand, improves antioxidant enzymes and anti-apoptotic molecules.Activating AMPK/mTOR-navigated autophagy and inhibiting NLRP3 inflammasome expression improved gastric ulcers evoked by ethanol [20].

Arabet al., 2022 established irbesartan and OM's individual efficacy in an in-vivo ethanol-induced gastric abrasion model by lowering oxidative, inflammatory, and apoptotic markers[178]. In addition to the antiulcer healing effect, irbesartan and OM administered orally downregulated nuclear NF-κBp65 protein levels, decreased NLRP3 inflammasome production, and mediated IL-1β. They both effectively removed aggregated SQSTM-1/p62 and increased Beclin 1, which is primarily associated with AMPK/mTOR pathway stimulation as indicated by increased AMPK (Ser487) phosphorylation and decreased mTOR (Ser2448) phosphorylation. Furthermore, irbesartan and OM had anti-oxidative and anti-apoptotic effects by lowering pro-oxidant levels, inhibiting Bax and caspase 3, and increasing antioxidant Nrf2 and Bcl-2.

They discovered that OM inhibits NFκB-NLRP3-mediated inflammation while activating the AMPK/mTOR pathway-driven autophagy[178]. Mohamed F. Balaha and co-scientists have indicated the antioxidative, anti-inflammatory, anti-apoptotic, and autophagy-inducing activities of amentoflavone orally for 14 days at 25, 50, or 100 mg/kg/day and OM in once oral instillation of 100 mg/kg indomethacin-induced gastric ulcer in 8-week-aged male Wistar rats (218). These protective benefits were attributable to enhanced autophagy in the stomach mucosa, as evidenced by higher levels of beclin-1, MAP1LC3B, and CTSD and decreased expression of p62 (SQSTM1). Also, these drugs altered the AMPK/mTOR pathway by raising p-AMPK and reducing mTORC1 levels. Furthermore, amentoflavone and OM altered the AMPK/mTOR pathway by raising p-AMPK and decreasing mTORC1 levels. Moreover, it reduced MDA levels while increasing SOD activity, GSH levels, and the Nrf2/HO-1 pathway.

Additionally, a decrease in caspase-3 levels, a decrease in the Bax/Bcl-2 ratio, and an increase in Bcl-2 expression show that the apoptotic process is inhibited. Both amentoflavone and OM attenuated gastric mucosal inflammation by dropping IL-1, TNF-, and IFN- levels, IL-4 and IL-6 mRNA expressions, and MPO activity while boosting IL-10 mRNA expression[195]. The anti-neuroinflammatory role of OM as autophagy induction and autophagy-mediated NLRP3 inflammasome suppression remains unknown.

Conclusion

Neuroinflammation is a multifaceted process triggered by various stressors, including infection, injury, and neurodegeneration. This review highlights the potential of Omeprazole (OM) as a therapeutic agent against neuroinflammatory conditions associated with neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), stroke, traumatic brain injury (TBI), among others. OM has demonstrated significant efficacy in reducing levels of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, thereby mitigating neuroinflammatory responses. Additionally, OM exhibits antioxidative properties by enhancing the activity of antioxidants like superoxide dismutase (SOD) and catalase while reducing pro-oxidant malondialdehyde (MDA) levels. Moreover, OM exerts its anti-inflammatory effects by modulating the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway, which is implicated in various inflammatory disorders, including gastrointestinal issues and renal injury. OM's neuroprotective mechanisms also involve suppressing excessive NMDA receptor activation-induced calcium influx, which disrupts cellular homeostasis and generates reactive oxygen species (ROS). By regulating mitochondrial function, OM reduces ROS production and preserves cellular integrity. Overall, OM shows promise as a therapeutic intervention in neuroinflammation by targeting multiple signaling pathways, including PPAR-γ, NF-κB, and Nrf2/HO-1. Further research and clinical trials are warranted to explore its full potential in combating neurodegenerative diseases and the associated neuroinflammatory processes.

Disclosure Statement

- **Ethical Approval:** Not applicable.
- **Availability of data and materials:** This declaration is not applicable. All the authors declare that all the figures used are novel.
- **Authors contributions:** Kartik Panbhare, Vrushali Neve, Pawan Karwa, and Deepali Kumari collected and Mold the information in the systematic review article. Pawan Karwa had listed out the table. RPB, PB, and Vrushali neve reviewed the article along with conclusions.
- **Conflict of Interest:** The authors declare that no conflicts of interest exist.
- **Funding source:** None.
- **Acknowledgments:** The author acknowledges the guiding faculty of Dr. D. Y. Patil Institute of Pharmaceutical Sciences and Research, Pimpri, Pune.

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