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Neuroinflammation Is Aggravated by the Aqueous Extract of *Myrmecodia platytyrea* Tuber

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Abstract

Background: *Myrmecodia platytyrea, commonly known as the ant plant, is a medicinal epiphyte traditionally used in Southeast Asia for its purported health benefits, including anti-inflammatory, antioxidant, antimicrobial, and anticancer activities. Its tuber contains abundant secondary metabolites, including flavonoids, tannins, phenolic compounds, and saponins. While these phytochemicals are generally associated with therapeutic effects, the biological activity of Myrmecodia extracts varies depending on the type of extract, dosage, and route of administration. In contrast to the commonly assumed anti-inflammatory properties of many plant-derived compounds, recent studies indicate that some aqueous extracts can produce unexpected or harmful effects under certain disease conditions. The influence of Myrmecodia platytyrea tuber extract on neuroinflammation remains largely unexplored.* ***Methods:*** *Astrocyte cytotoxicity was assessed using the MTT assay. The impact of MPAE at concentrations between 0.025 and 0.5 mg/mL was evaluated on reactive oxygen species (ROS) generation and the secretion of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) in astrocyte cultures stimulated with Fe_2SO_4, H_2O_2, and LPS.* ***Results:*** *MPAE exhibited no cytotoxic effects on astrocytes under baseline conditions. However, it failed to confer protection against oxidative or inflammatory stress induced by Fe_2SO_4, H_2O_2, or LPS. In contrast, MPAE treatment led to increased astrocyte death and elevated ROS and cytokine levels in a dose-dependent fashion.* ***Conclusion:*** *While MPAE does not exhibit inherent cytotoxicity, its ability to amplify neuroinflammation in vitro raises important safety concerns – particularly for elderly individuals using this plant to alleviate inflammatory symptoms. These findings underline the necessity for further in-depth research to assess its safety and therapeutic potential before considering it for neurodegenerative disease treatment.*

Keywords: Astrocytes, neuroinflammation, oxidative stress, pro-oxidant, *Myrmecodia platytyrea*

INTRODUCTION

Historically, the substantial contributions of natural products and their structural analogues to pharmacotherapy cannot be overlooked. Their role in treating chronic ailments, including infectious diseases and cancer, is pivotal. However, due to difficulties with isolation, screening, characterization, and optimization, the pharmaceutical industry's interest in these natural products started to decline in the 1990s. These natural products, particularly those derived from traditional medicinal plants, have attracted renewed attention in recent years as possible treatments for diseases linked to inflammation [1, 2]. Particularly in developing nations, medicinal plants are particularly appealing due to their accessibility, affordability, and historical effectiveness. A progressive loss of cognitive, physical, and social abilities is a hallmark of neurodegenerative diseases, a group of brain conditions that include Alzheimer's (AD), Parkinson's (PD), Huntington's (HD), and amyotrophic lateral sclerosis. The quality of life is severely reduced by these illnesses, which have their

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roots in neuroinflammation and long-term oxidative stress [3, 4]. The brain's high oxygen consumption and polyunsaturated fatty acid enrichment make it more susceptible to oxidative stress [5–7]. The importance of metabolic coupling between neurons and astrocytes in preventing brain oxidative stress is highlighted by this vulnerability [8, 9]. As the primary modulators of neuroinflammation, astrocytes are essential for neurogenesis and brain pathology [10], as well as for preserving the central nervous system's (CNS) health and functionality [11]. Given their diverse range of functions, it is not surprising that these cells are connected to the development and course of several neurodegenerative diseases [12–15]. Astrocytes are suitable as *Invitro* models for neurodegenerative diseases [16–18], as evidenced by recent studies that highlight their protective functions against free-radical toxicity and their responsiveness to inflammatory signals [14, 15].

Curcumin, resveratrol, alkaloids, flavonoids, and other natural compounds are showing promise as multitarget treatments for neurodegenerative diseases because of their varied qualities. The *Myrmecodia platytyrea,* also known as ant-plant or Sarang Semut, is well-known in traditional medicine for its anti-inflammatory, anti-cancer, and antioxidant qualities [19–21]. This plant's tuber is abundant in bioactive substances, like flavonoids, tannins, polyphenols, and stigmasterol, all of which enhance its potential for therapeutic use [19, 22, 23]. One of *M. platytyrea*'s primary bioactive groups, flavonoids, are notable for their capacity to penetrate the blood–brain barrier (BBB) and have neuroprotective properties. These substances exhibit anti-inflammatory and antioxidant qualities, which are essential for reducing neuroinflammation and oxidative stress in the central nervous system [24–26]. Although *Myrmecodia sp.* decoction has been used traditionally to treat inflammation-related conditions, little is known about how it specifically affects neuroinflammation and whether it can be used to treat neurodegenerative diseases. Clarifying the neuroprotective effects of (MPAE) on nerve cells, with an emphasis on its potential to prevent or mitigate neuroinflammatory processes, is the goal of this study.

METHODS

Plant Extraction

M. platytyrea tubers were identified by Dr. Anil Chauhan after being gathered from the Centre for Aromatic Plants (CAP) in the industrial area of Selaqui, Dehradun. Dr. Chauhan is heading Centre for Aromatic Plants (CAP), Selaqui, Dehradun as a director since April 2017 earlier he was scientist-in-Charge in the same institution. cA decoction technique was used in this investigation [27]. In short, the dried *M. platytyrea* tuber was ground into a powder, soaked in boiling distilled water (1:9) for 15 minutes, and then filtered through four different types of filter paper, including cellulose acetate membrane filters and Whatman No. 1, 40, and 42. Using a rotary evaporator (Heidolph, Germany) at 100 mbar and 55°C with reduced pressure, the solvent in the filtrate was removed. After two days of storage at –80°C, the concentrated filtrate was freeze–dried in a freeze–dryer at a pressure of 0.007 mbar to produce the dried powder of aqueous extract. Before being used, the powdered extract was stored at –20°C.

Astrocyte Culture

The C8-D1A (ATCC® CRL 2541™) murine astrocyte cell lines were acquired from lifetechindia.com › primary-cells › human–astrocytes. | Life Technologies (India) Pvt. Ltd. | Human Astrocytes Cells. The C8-D1A cell line was isolated from the cerebellum of the mouse (Mus musculus sp.) brain and resembles fibrous astrocytes. Foetal bovine serum (FBS; Thermofisher, UK) was added to Dulbecco's Modified Eagle's Medium (DMEM; Sigma–Aldrich) to a final concentration of 10% in a 75 cm^3 flask, which served as the cell line's entire growth medium.

Cytotoxicity of MPAE

Once confluent, MPAE was tested on the cells for cytotoxicity study using MTT assay [28]. Cells (100 µL) were seeded into each 96-multiwell plate (Corning, Sigma, USA). After 24 h, the MPAE extracts (0.0001, 0.001, 0.01, 0.1, 1, and 10 mg/mL) were added into the wells and incubated for 24, 48 or 72 h. At the end of each incubation period, 20 µL of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT; Sigma–Aldrich) solution was added to each well. After 4 h of incubation, the supernatant was removed, and 100 µL of DMSO was added into the wells to dissolve the formazon. MTT reduction was quantified at 550 nm using a microplate reader (Infinite M200, Tecan, Switzerland).

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Determination of the Effect of MPAE on Cell Viability Activity of Fe_2SO_4- and H_2O_2-Induced Oxidative Stress and LPS-Induced Inflammation on Astrocytes

Astrocytes (2×10^4 cells/well) were seeded in a 96well plate and incubated for 24 h. Then, the plated cells were treated with MPAE extract (i.e., 25, 50,125, 250, and 500 µg/mL) for 1 h. After that, the media containing Fe_2SO_4 (7.5 mM), H_2O_2 (0.2 mM) and LPS (1 µg/mL), respectively, were added into each well and then incubated at 37°C, 5 % CO_2 for 24 h. Then, the MTT assay was carried out. Cell viability was determined after a 4-h incubation by measuring the absorbance at 550 nm using a microplate reader (Infinite M200 Tecan, Switzerland).

Determination of the Effect of MPAE on Reactive Oxygen Species (ROS) Level in Fe_2SO_4- and H_2O_2-Induced Oxidative Stress

The fluorescent probe 2',7'-dichlorofluorescein diacetate (DCF-DA) was used to measure the accumulation of ROS [29]. After being seeded in a 96-well black plate, astrocytes (2 × 104 cells/well) were incubated for 24 hours. Following a 1-hour treatment with varying concentrations of MPAE extract (i.e, 25, 50, 125, 250, and 500 µg/mL), the plate was incubated for 24 hours with either Fe_2SO_4 (7.5 mM) or H_2O_2 (0.2 mM). Kreb's buffer was then used to wash the cells. Next, 100 µL of a 5 µM DCF-DA solution was added to each well in the dark to begin the measurement. ROS production was measured using a microplate reader at Ex = 485 and Em = 538 nm following 30 minutes of incubation at 37ºC.

Determination of Effect of MP on Pro-Inflammatory Cytokines of LPS-Induced Astrocytes

A 6-well plate was seeded with 5 × 105 cells/well of astrocytes for 24 hours prior to treatment with MPAE (25, 50, 125, 250, and 500 µg/mL). A 24-hour incubation period was then followed by the addition of LPS (1 µg/mL) to the cells [9].

On 96-well plates, astrocytes (2 × 104 cells/well) were seeded, and they were incubated for 24 hours with MPAE (0.001, 0.01, 0.1, 1, and 10 mg/mL). The MTT assay was used to assess cell viability. Average ± standard deviation (n = 3). The MPAE IC50 was 1.54 ± 0.26 mg/mL.

Cells were subsequently harvested and centrifuged at 3000 rpm for 10 minutes at 4ºC. The levels of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6, were assessed using an ELISA kit. All assays were performed following the manufacturer's instructions. Absorbance readings were obtained using a microplate reader (Infinite M200, Tecan).

Statistical Analysis

Data are expressed as the mean ± standard deviation (SD) from three independent replicates. Statistical analysis was conducted using one-way ANOVA with GraphPad Prism 7 software. Group comparisons were further evaluated using the Bonferroni post hoc test. A p-value of less than 0.05 was considered to indicate statistical significance.

RESULTS

The tubers of *M. platytyrea* were processed into an aqueous extract using the decoction method to mimic traditional medicinal preparation. The extraction resulted in a yield of 16.05 ± 0.14%.

The C8-D1A murine astrocyte cell line was used as the cell model to depict CNS functions because these cells are important for both the pathological process and physiological neuronal functions. MPAE is not cytotoxic to normal astrocyte cell lines, as demonstrated by the MTT assay, which showed an IC50 of 1.54 ± 0.26 mg/mL in astrocytes (Figure 1) and a maximal inhibition of 81.40 ± 2.33% at 10 mg/mL. Cytotoxicity is categorized using the following criteria: High cytotoxicity is defined as IC50 < 20 µg/mL, mo derates cytotoxicity as IC50 21–200 µg/mL, weak cytotoxicity as IC50 201–500 µg/mL, and no cytotoxic activity as IC50 >501 µg/mL [30].

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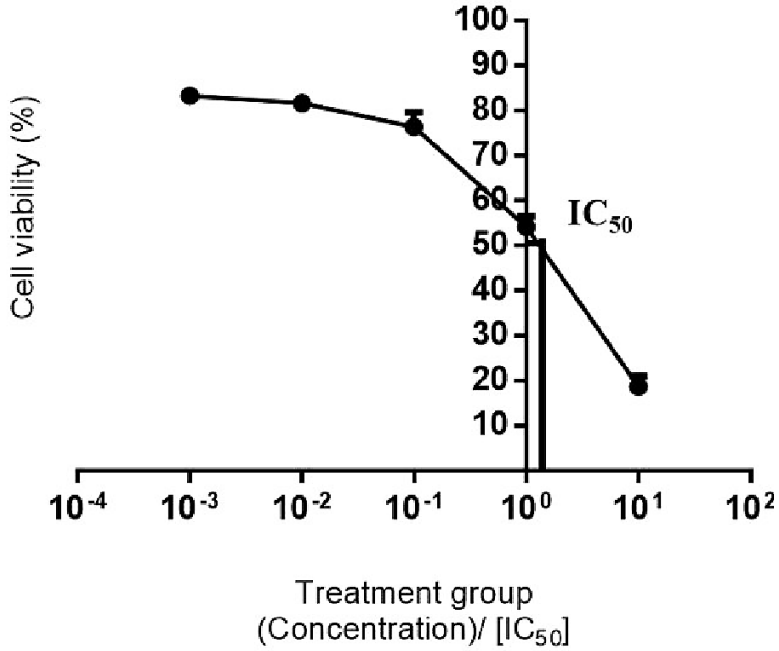

Figure 1. Effect of *M. platytyrea* tuber aqueous extract on astrocyte viability.

MPAE's impact on astrocyte viability was assessed for 24 hours in oxidative and inflammatory conditions brought on by Fe_2SO_4, H_2O_2, or LPS (Figure 2). Astrocyte viability was significantly ($P < 0.05$) decreased by exposure to Fe_2SO_4 (7.5 mM), H_2O_2 (0.2 mM), and LPS (0.1 µg/mL) to 51.39 ± 4.63% (Figure 2A), 52.25 ± 0.6% (Figure 2B), and 70.1 ± 3.4% (Figure 2C), respectively. For all three inducers, pretreatment with MPAE (25, 50, 125, 250, and 500 µg/mL) worsened the decrease in cell viability in a concentration-dependent manner ($P < 0.05$). There was no evidence of cytoprotection by MPAE; rather, cell viability declined even more.

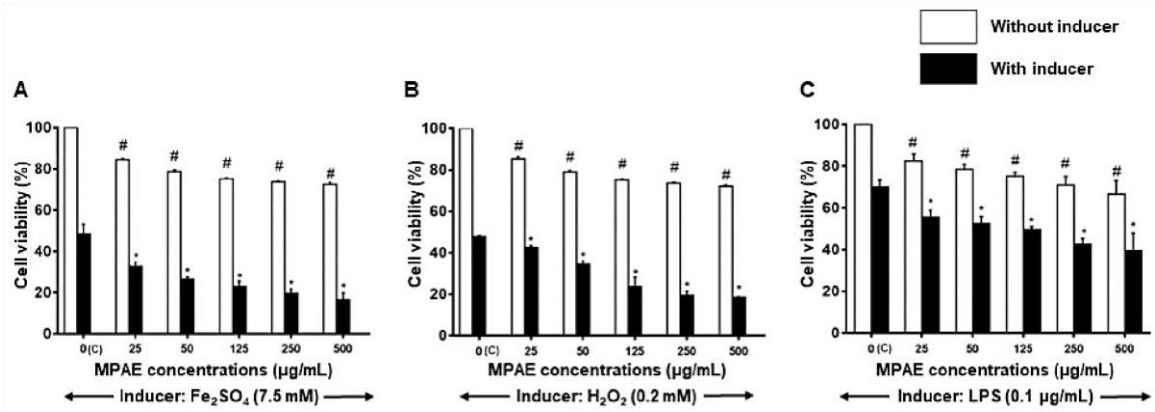

Figure 2. MPAE's effects on astrocyte viability after induction with (A) Fe_2SO_4, (B) H_2O_2, and (C) LPS.

The DCF-DA assay was used to quantify the amount of ROS present in the astrocytes (Figure 3). When compared to control cells, ROS production was significantly increased by 4.70 ± 0.83 times with Fe_2SO_4 (7.5 mM) alone ($P < 0.05$, Figure 3A). With fold changes ranging from 4.75 ± 0.33 to 5.7 ± 1.66 when compared to cells treated with Fe_2SO_4 alone, pretreatment with MPAE (25–500 µg/mL) did not significantly change ROS levels in cells treated with Fe_2SO_4 ($P > 0.05$).

Using the MTT assay, cell viability was assessed. Mean ± SD (n = 3). Significantly different from cells treated with MPAE and the inducer agent alone ($P < 0.05$, One-way ANOVA + Bonferroni test) and from control cells that did not receive either treatment.

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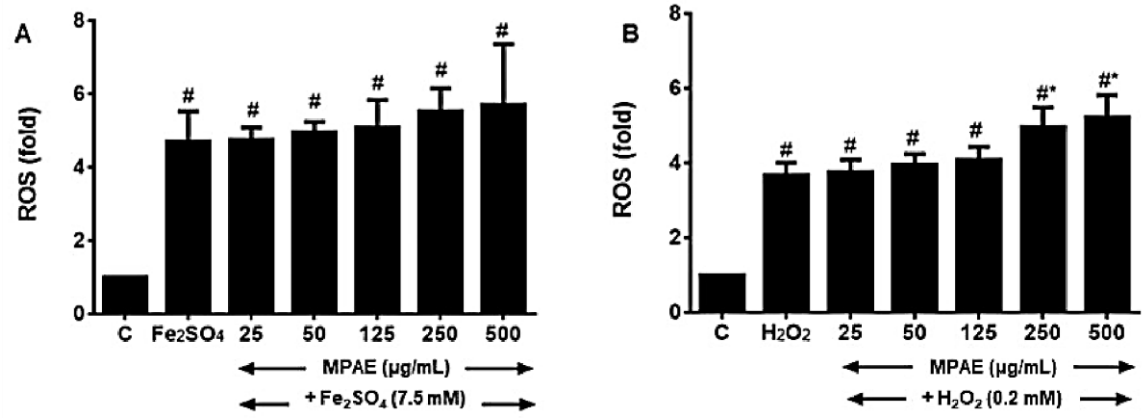

Figure 3. Effect of MPAE on ROS production by astrocytes exposed to (A) Fe_2SO_4- or (B) H_2O_2-induced oxidative stress.

DCF-DA assay was used to determine ROS. Average ± standard deviation (n = 3). # markedly distinct from control cells that did not receive MPAE or an inducer agent treatment notably different from cells that were only exposed to the inducer agent. ROS production by Fe_2SO_4 or H_2O_2 was unaffected by MPAE pretreatment of cells ($P > 0.05$, One-way ANOVA + Bonferroni test).

By using the ELISA assay, cytokines were identified. Mean ± SD (n = 3). Similar to control cells, ROS production was significantly increased by 3.7 ± 0.3 times when H_2O_2 (0.2 mM) was present ($p < 0.05$, Figure 3B). MPAE pretreatment (25–500 µg/mL) raised ROS production even more, especially at higher concentrations (250 and 500 µg/mL), which resulted in increases of 5.0 ± 0.5 and 5.2 ± 0.6 times, respectively ($P < 0.05$). This shows that ROS buildup in cells treated with H_2O_2 was worsened by higher MPAE concentrations. The levels of TNF-α (45.78 ± 9.61 pg/mL, Figure 4A), IL-1β (94.7 ± 5.8 pg/mL, Figure 4B), and IL-6 (121.0 ± 18.0 pg/mL, Figure 4C) were significantly higher in LPS (1 µg/mL) than in control cells ($P < 0.05$). These cytokine levels were further raised in a concentration-dependent manner by pretreatment with MPAE. At 250 and 500 µg/mL of MPAE, there were notable increases in TNF-α and IL-6 above and beyond LPS alone ($P < 0.05$, Figure 4A and C). Furthermore, compared to LPS alone, MPAE concentrations of 125, 250, and 500 µg/mL markedly raised IL-1β levels ($P < 0.05$, Figure 4B).

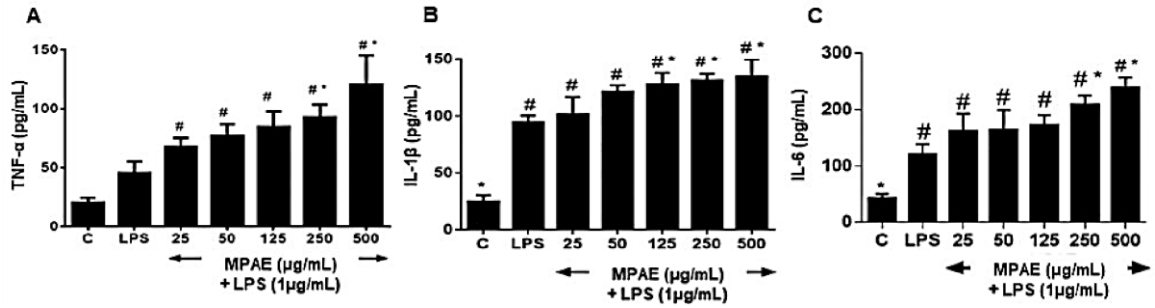

Figure 4. Effect of MPAE on (A) TNF-α, (B) IL-1β and (C) IL-6 levels of astrocytes exposed to LPS-induced inflammation.

DISCUSSION

Organic solvent extracts (such as methanol, acetone, chloroform, dichloromethane, etc.) are very likely to cause toxicity, whereas aqueous extraction was chosen because it is safe for ingestion [31]. Additionally, depending on the solvent's polarity, other extraction techniques might only retain a portion of the plant material's compounds, whereas aqueous extraction preserves all of them [32]. A model of oxidative stress was developed by using Fe_2SO_4 to induce iron overload in astrocytes. Iron overload can occur in AD, PD, and HD [33–35] and raises synaptic activity, which can have cytotoxic

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effects [31, 32]. MPAE has good chelating activity, with an IC50 of 147.62 ± 18.82 µg/mL, according to a preliminary study conducted by a colleague who examined its effect on the ferrous–ion chelating (FIC) assay [36]. Moreover, *M. platytyrea* tuber extracts can lower cytokine levels in HepG2 cells and inhibit ROS production [36]. Nonetheless, MPAE increased cell death in this study in a concentration-dependent manner and had no protective effect on astrocytes against Fe_2SO_4 assault. The second model of oxidative stress was brought on by H_2O_2.

Excess H_2O_2 functions as a signaling mechanism to initiate the cellular apoptotic pathway or directly oxidizes lipids, proteins, and DNA, which both cause cell damage [37, 38]. The cell viability significantly decreased when 0.2 mM H_2O_2 was used to induce astrocytes. MPAE pretreatment dramatically accelerated cell death in comparison to untreated cells and boosted the oxidative stress response in astrocytes. Because MPAE contains a lot of antioxidants, it may have acted as a pro-oxidant when H_2O_2 was present, causing oxidative stress by either inhibiting antioxidants or producing ROS. Antioxidants known as free radical scavengers can also be pro-oxidants if they are not connected to a radical sink. When an antioxidant radical is a radical sink, it must "sink" its unpaired electron in other reactions. Ascorbic acid, vitamin E, and polyphenols are examples of antioxidants that function as pro-oxidants when transition metals are present [39]. For instance, when Cu_2^+ ions are present, resveratrol encourages oxidative DNA damage, which could be problematic as a neuroprotectant [40]. Because of its exceptionally high antioxidant activity, MPAE may have converted its antioxidative action to pro-oxidant action. Some common and well-known antioxidant flavonoids actually have pro-oxidant properties, which is surprising [41]. The "double-edge sword" action was generally triggered by the presence of metal ions and was influenced by the compounds' chemical structures in MPAE [42, 43]. The ability of flavonoids to donate electrons may be linked to their antioxidant properties through the hydroxyl (OH) functional group [44, 45]. There is no antioxidant or Fe/Cu-initiated pro-oxidant activity in polyphenols without OH groups such as flavone and flavanone. Fe/Cu-initiated pro-oxidant activity in flavonoids is dependent on the number of free OH groups present [34, 46]. Pro-oxidant activity rises when OH groups are present. Prooxidant and antioxidant activity of flavonoid OH groups is inactivated by O-methylation and possibly other O-substitutions [39, 47]. Thus, ROS, including H_2O_2, are produced by pro-oxidant activity in the astrocytes. Overexposure to H_2O_2 results in oxidative–nitrosative stress, which damages cells by oxidizing proteins, lipids, and DNA [48, 49]. H_2O_2 overload causes mitochondrial membrane potential dysfunction, morphological changes, and apoptotic cell death by increasing the expression of inducible nitric oxide synthase (iNOS), releasing cytokines (TNF-α, IL-1β, IL-1, and IL-6), and decreasing antioxidant defense (SOD, CAT, and GPx) [50, 51]. On the other hand, blocking these mediators can lessen neuronal damage [50].

Astrocytes were incubated with 0.1 µg/mL LPS, which resulted in roughly 26% cell death, to create a model of neuroinflammation. 0.1 µg/mL of LPS has been used in a few studies to successfully cause inflammation in astrocytes, but there has been no discernible toxic effect (~25–30% cell death) [9, 42, 43]. By raising cytokine production and the level of glial fibrillary acidic protein (GFAP), which influences TLR-4 expression, 0.1 µg/mL of LPS also activates astrocytes, according to a prior study [9].

MPAE pretreatment of LPS-induced astrocytes caused the release of cytokines. Pro-inflammatory signaling cascades, including NF-κβ and mitogen-activated protein kinase (MAPK), are activated to start inflammation [44]. TNF-α and interleukins are examples of pro-inflammatory cytokines that are stimulated by activated NFκβ and whose release causes inflammation and necrosis, which leads to cell death [45]. The higher loss of cell viability in this study when MPAE was present demonstrated this. Therefore, in the presence of inducers, MPAE treatment increases oxidative damage and inflammation, which in turn increases cell death.

The decoction of *M. platytyrea* tuber is claimed by the indigenous people of Papua New Guinea as an anticancer remedy [20]. The effectiveness of this tuber has been investigated in a few studies, which suggested that it may be used to treat diabetes and cancer, as well as to inhibit pain, which are diseases linked to inflammation [20, 21]. As previously mentioned, phenolic compounds (flavonoids, terpenoids,

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and anthocyanins) and phytosterols (stigmasterol and β-sitosterol) were thought to be responsible for the tuber's advantages [19, 22–23, 46, 48]. These substances have potent anti-inflammatory and antioxidant qualities.

Protein processing abnormalities, genetic disorders, misfolding and aggregation of different proteins, cellular apoptosis, mitochondrial dysfunction, neuroinflammation, free radical production, and oxidative stress seem to be the main causes of neurodegeneration [49]. There are excellent chances that *M. platytyrea* will be able to reduce the occurrence of neurodegenerative diseases in the aging population because the compounds found in its tuber have the ability to inhibit neuroinflammation and block oxidative stress.

MPAE's "double-edged sword" action exacerbated oxidative stress and neuroinflammation. The high levels of phenolic antioxidant compounds in the rich antioxidant MPAE may increase damage due to pro-oxidant activity when inducers are present.

Flavonoids, such as kaempferol, luteolin, apigenin, and quercetin, and phenolic compounds, such as rosmarinic acid, procyanidin B1, and polymer of procyanidin B1, are found in myrmecophytes [50]. Bioactive substances with a strong antioxidant capacity, including stigmasterol and morindolide, are found in *M. platytyrea* tubers [23]. However, MPAE functioned in the astrocytes in this investigation in a distinct way.

The findings of several studies on antioxidants are debatable. The balance between the beneficial and detrimental effects of antioxidants may be influenced by their type, dosage, and matrix [37, 51]. On healthy cells, pro-oxidant activity causes lipid peroxidation and apoptosis as a result of cell death and damages biomolecules like DNA, proteins, and lipids [52]. Additionally, it has the ability to start an intracellular signaling pathway that raises the production of pro-inflammatory cytokines, which causes inflammation [53]. The MPAE's high polyphenolic content suggests that it has "double-edged sword" properties, acting as either pro-oxidants or antioxidants based on metal ion presence or concentration/doses [54]. Therefore, the proposed mechanism of action of MPAE in astrocytes (Figure 5). However, because microglia were not employed in the investigation, this study had limitations. Comparing the results from the two cell types could lead to a more thorough understanding and approach to treating neuroinflammatory diseases. Additionally, it is advised that MPAE's effects be expanded to in vivo research to gain a deeper understanding of the complex causes of neurodegenerative illnesses like AD and PD.

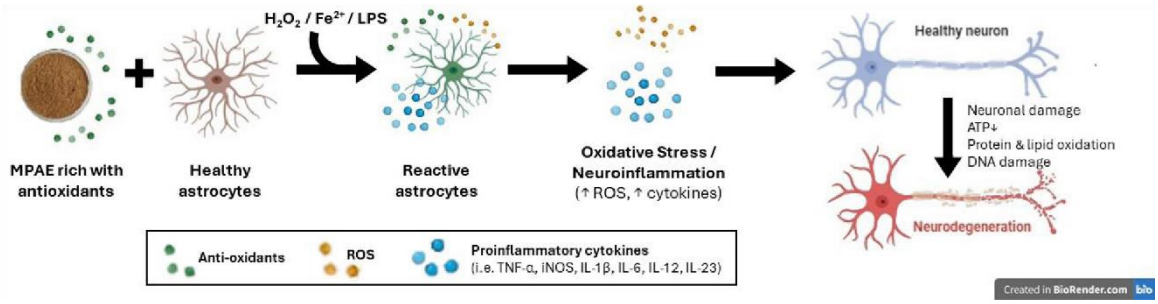

Figure 5. Plausible mechanism of action of MPAE on astrocytes exposed to hydrogen peroxide/iron (II) sulphate/lipopolysaccharide that leads to neuronal damage.

CONCLUSIONS

This is the first study that we are aware of that looks at how MPAE affects neuroinflammation. MPAE's "double-edged sword" mechanism may have contributed to the dose-dependent cytotoxicity and increased ROS and cytokine levels observed in astrocytes after pretreatment. Although MPAE is not cytotoxic to astrocytes, its ability to exacerbate neuroinflammation *in vitro* raises questions about its use, particularly in older people who use the plant to treat inflammatory conditions. These results

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highlight the need for caution before recommending its therapeutic use, especially for treating neurodegenerative diseases, and emphasize the importance of additional research to evaluate its efficacy and safety. To determine which MPAE compounds worsen oxidative stress and inflammation in the astrocytes, more research is necessary.

DECLARATIONS

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Availability of Data and Materials

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Conflicts of Interest

All authors declare that there are no competing interests.

Ethical Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Assay	Purpose	Outcome
3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay	To assess cell viability.	Dose-dependent response.
Lipopolysaccharide (LPS) stimulation	To induce neuroinflammatory response.	Elevated pro-inflammatory markers.

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