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Review Article

A Review on Microglia in Neurodegenerative Disorders: An Overview of Natural Products in the Treatment of Neurodegenerative Disease by Targeting Arginase 1

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ABSTRACT

This review offers an overview of the crucial role microglia play in neurodegenerative disorders such as Alzheimer's, Parkinson's and Huntington's diseases. It also delves into the therapeutic potential of natural products targeting Arginase-1 and L-arginine for treating these conditions. As key immune cells in the brain, microglia significantly contribute to the onset and progression of neuroinflammation, which is closely associated with neurodegeneration. The paper elucidates the intricate interplay between microglial activation, neuroinflammation and the development and progression of neurodegenerative diseases. This review primarily examines the shift of microglial polarization from a pro-inflammatory (M1) to an anti-inflammatory (M2) state, highlighting it as a promising therapeutic approach for treating neurodegenerative diseases. Specifically, the regulation of Arginase-1 and its substrate, L-arginine, within microglia presents a novel avenue for intervention. The review highlights the potential of natural products such as resveratrol, piceatannol, epicatechin, curcumin, sulforaphane, flavonoids and cannabidiol, ginsenosides in influencing microglial function by targeting Arginase-1 and L-arginine metabolism. By targeting Arginase-1, natural products have shown promise in modulating microglial activation and shifting the balance towards an anti-inflammatory phenotype, thereby mitigating neuroinflammation and subsequent neurodegeneration. Moreover, the review underscores the importance of comprehending the molecular processes that drive the effects of these natural products. on microglial function, particularly their impact on Arginase-1 and L-arginine metabolism. In conclusion, this review emphasizes the therapeutic potential of natural products targeting Arginase-1 and L-arginine in the treatment of neurodegenerative diseases by modulating microglial activation and neuroinflammation.

Keywords: Arginase-1, Microglia, Neurodegenerative Diseases.

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INTRODUCTION

For many years, scientists thought the brain was composed solely of neurons. Neurons are the basic building blocks of the brain, responsible for receiving, transmitting and processing information. However, at the start of the last century, Santiago Ramón y Cajal referred to microglia as the 3rd element of nerve centers (Del Río-Hortega, 2020). A few years afterward, his student Pio del Rio-Hortega coined their present name and found that non-neuronal cells, known as glia, constitute half the mass of our brain. Micro-from micro (small) and glia (glue), are generally smaller but are more abundant than neurons (Goudarzi, 2016). Microglia are present throughout the Central Nervous System (CNS), with varying densities in different regions. Typically, the white matter has fewer microglia than the grey matter. Overall, microglia constitute between 0.5% and 16.6% of the total cell population in the human brain (Sabogal-Guáqueta *et al.*, 2020). Under normal physiological conditions, the number of microglia is tightly regulated by local cells and the surrounding microenvironment. Each neuron is supported by roughly 10 to 50 glial cells (Sabogal-Guáqueta *et al.*, 2020).

The Blood-Brain Barrier (BBB) is a semi permeable layer that prevents pathogens from entering our brains However, BBB limits the entry of immune mediators into CNS to combat illnesses. Nevertheless, microglia, being the specialized immune cells in the brain, play a crucial role in bolstering the brain's defence mechanisms by responding to harmful agents that manage to breach the BBB (Bennett *et al.*, 2018). In addition, microglia undertake numerous vital maintenance roles such as phagocytic

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clearance of neurons with impaired synaptic transmission. Microglia originate from myeloid progenitors in the embryonic yolk sac, migrate to the brain and proliferate during development. Hence, they then acquire plastic ability to mature into distinct phenotypes like the peripheral macrophage, upon exposure to extrinsic cues (physiological and pathological conditions) in CNS (Mendes and Majewska, 2021).

Generally, there are three states of microglia: (Figure 1) resting, activated microglia and phagocytic microglia (Boche *et al.*, 2013). Resting microglia are characterized by a highly branched shape and actively monitor the central nervous system without being exposed to inflammation (Arcuri *et al.*, 2017; Sanguino-Gómez *et al.*, 2022). They form connections with neurons, constantly survey their surroundings and contribute to functions like synaptic maintenance and surveillance (Arcuri *et al.*, 2017; Sanguino-Gómez *et al.*, 2022). Upon stimulation, microglia undergo a transformation where their processes retract and thicken, transitioning from a ramified state to an intermediate 'bushy' state and eventually adopting an amoeboid state (Sanguino-Gómez *et al.*, 2022). Activated microglia release inflammatory molecules, increase the permeability of the blood-brain barrier and recruit immune cells from outside the brain, promoting neuroinflammation. Activated microglia are involved in processes such as phagocytosis and antigen presentation. Phagocytic microglia are a specialized subset that actively remove cellular debris, pathogens, or harmful substances, crucial for tissue maintenance (Sanguino-Gómez *et al.*, 2022). Activated microglia show heightened expression of distinct markers such as ionized calcium-binding adaptor molecule-1 (Iba-1), Major Histocompatibility Complex antigen class II (MHC-II) and various phagocytic markers including CD11b, complement and Fc receptors I-III and CD68 (Jurga *et al.*, 2020; Yuan *et al.*, 2019). Additionally, these activated cells can adopt different functional states, which can either be neurotoxic or neuroprotective. These states are marked by the release of both pro-inflammatory and anti-inflammatory mediators and cytokines, respectively (Sochocka *et al.*, 2017).

For years microglial research has been stalled by the false impression that these cells only functioned as macrophages in the neuroinflammatory response. Exposure to stress factors such as aging, stroke, infections, toxins, or specific medications can trigger neuroinflammation. Neuroinflammation aims to repair damaged glial cells and neurons within the central nervous system (Kempuraj *et al.*, 2016). However, prolonged or excessive exposure can have adverse effects, inhibiting neuronal regeneration and promoting pathological conditions like dysfunction, injury and even death (Kempuraj *et al.*, 2016). In recent years, neurodegenerative disorders like Alzheimer's, Parkinson's and amyotrophic lateral sclerosis have emerged as significant burdens on individuals and society worldwide. Therefore, it is essential to understand interplay between various neuro-immune and inflammatory mechanisms and explore their mechanistic underpinnings for developing therapeutic approaches to alleviate neurodegeneration across various neurological conditions.

Microglia in Neuroinflammation and Neurodegenerative Disorders

Microglia are pivotal players in neurodegenerative disorders, influencing both the upkeep and protection of the Central Nervous System (CNS), while also associated in neuroinflammation and neuronal degeneration. These specialized cells serve three main roles: vigilant surveillance of the CNS environment, maintenance of neuronal health and function and defence against changes to provide neuroprotection (Hickman *et al.*, 2018). However, in neurodegenerative diseases, microglia can become activated and contribute to neuronal harm (Hickman *et al.*, 2018). This activation typically stems from disruptions in their surveillance and maintenance functions, leading to dysregulation in their defence mechanisms (Hickman *et al.*, 2018). Different pathways, such as Trem2, C×3cr1 and progranulin, act as immune checkpoints that regulate inflammatory responses, while scavenger receptor pathways assist in clearing harmful agents (Kempuraj *et al.*, 2016). Additionally, microglia have the ability to regulate neuroinflammation through diverse tactics such as suppressing the synthesis of microglial exosomes, modifying metabolism, altering the microglial phenotype, activating Trem2 receptors and others (Gao *et al.*, 2023). These approaches are under investigation as potential therapeutic avenues for addressing neurodegenerative conditions.

Understanding the equilibrium among the various roles of microglia is essential in addressing neurodegeneration. By regulating imbalances in activity of microglia there is potential for the development of innovative therapies targeting microglia to mitigate the progression of neurodegenerative diseases. Under normal circumstances, microglia remain dormant, but they activate in response to Pathogen-Associated Molecular Patterns (PAMPs) or endogenous Damage-Associated Molecular Patterns (DAMPs) (Hernández-Pedro *et al.*, 2016). Upon activation, microglia release inflammatory molecules, enhance BBB permeability and recruit peripheral immune cells into the brain, leading to neuroinflammation. This activation can result in various phenotypes of microglia, including M1 and M2 (Figure 2), each exhibiting distinct markers, secreting different compounds and performing diverse functions. The complexity of microglial activation extends beyond the traditional M1/M2 classification, highlighting their multifaceted roles in neuroinflammation (Laurindo *et al.*, 2024).

M1 microglias are known for their pro-inflammatory characteristics and typically become activated in response to stimuli like Interferon-gamma (IFNγ) or Lipopolysaccharide (LPS) (Figure 2). When in the M1 state, these microglia release pro-inflammatory cytokines such as Tumor Necrosis Factor

alpha (TNFα), Interleukin-6 (IL-6) and IL-1β, contributing to neuroinflammation (Laurindo *et al*., 2024; Cunha *et al*., 2016; Lively and Schlichter, 2018). While microglia play a role in fighting pathogens and clearing cellular debris, prolonged or dysregulated activation of M1 microglia can result in tissue damage and neuronal death. In contrast, M2 microglia display anti-inflammatory characteristics and promote neuroprotection. They become activated in response to Interleukin-4 (IL-4) or Interleukin-13 (IL-13) and are involved in tissue repair, inflammation resolution and promoting neuroprotection. M2 microglia release anti-inflammatory cytokines and growth factors that promote neuronal survival and repair processes, contributing to tissue homeostasis (Laurindo *et al*., 2024; Cunha *et al*., 2016; Lively and Schlichter, 2018). It's worth noting that M1 and M2 phenotypes represent opposite ends of microglial activation and in reality, microglia can display a spectrum of activation states with mixed characteristics. This complexity highlights how microglial activation is dynamic, allowing them to respond and adapt to different stimuli within the central nervous system, impacting both normal functions and disease processes.

ROLE OF ARGINASE IN NEURODEGENERATIVE DISEASES

Arginase 1 (Arg1) plays a pivotal role in regulating Nitric Oxide (NO) production by competing with Nitric Oxide Synthase (NOS) for their shared substrate, L-arginine (Keshet and Erez, 2018). This competition helps maintain balanced NO levels crucial for various physiological functions such as neurotransmission and neurovascular regulation (Lourenço and Laranjinha, 2021). Arg1 activity is associated with tissue repair and regeneration, promoting cell growth, collagen synthesis and neuronal development in response to injury or stress. Proper Arg1 function is essential for cellular processes supporting neuronal health and development, particularly significant in neurodegenerative disorders (Kwon and Koh, 2020). Arg1 can modulate immune responses by promoting the anti-inflammatory M2 phenotype in microglia (Figure 2), potentially reducing neuroinflammation, which is a hallmark of conditions such as Alzheimer's and Parkinson's diseases (Kwon and Koh, 2020).

In such neurodegenerative diseases, studies have focused on Arg1+microglia, revealing their correlation with disease onset and progression. These microglia play an important role in shaping cognition and memory, especially notable in female mice. Research has explored microglia, including Arg1+microglia, across many neurodegenerative disorders. Highlighting their diverse functions in different pathological conditions (Zhang *et al*., 2023). Studies indicate that Arg1+microglia, characterized by their alternative activation, reduce Amyloid-beta (Aβ) plaque deposition during sustained neuroinflammation, potentially benefiting Alzheimer's disease pathology (Cherry *et al*., 2015). These microglia exhibit anti-inflammatory properties associated with Aβ plaque reduction, suggesting a therapeutic potential in mitigating Aβ pathology. Upregulation of centrally derived Arg1+microglia during neuroinflammation correlates with increased plaque clearance, emphasizing their role in reducing Aβ pathology (Cherry *et al*., 2015). Inducing Arg1+microglia with IL-4 shows significant plaque clearance, indicating the therapeutic potential of targeting arginase to modulate microglial responses and Aβ pathology (Cherry *et al*., 2015). A study by Ma *et al*. (2021), underscored the impact of myeloid Arg1 insufficiency on exacerbating amyloid-beta-associated neurodegenerative pathways and glial signatures in an Alzheimer's disease mouse

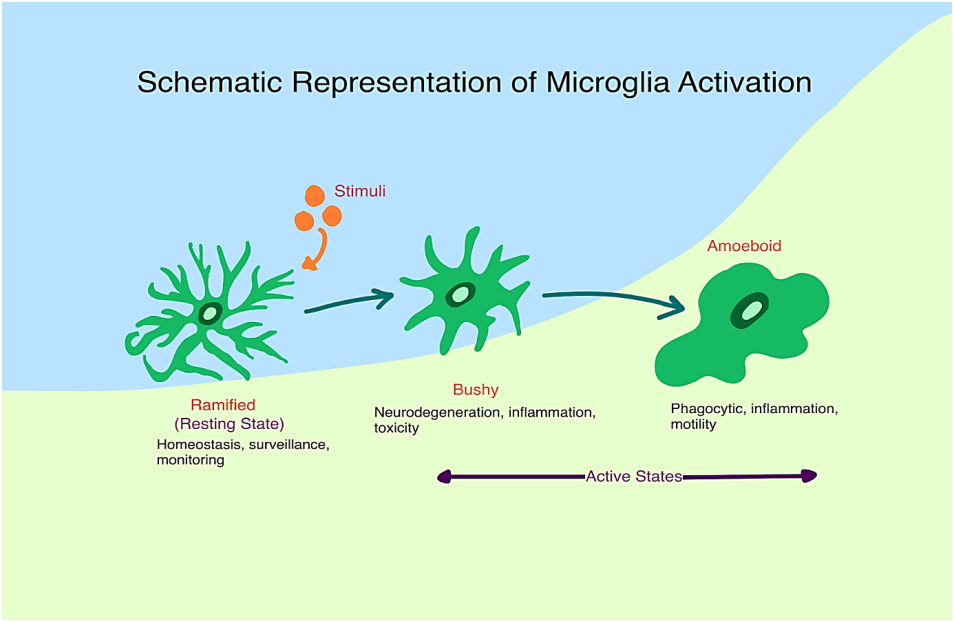

Figure 1: Schematic representation of Microglia activation when exposed to stimuli. Their morphological variation and the intensity of its activity depends on its stress conditions.

model. The findings highlighted the critical role of proper Arg1 function in normal and pathological conditions related to Alzheimer's disease (Ma *et al*., 2021).

The precise involvement of Arg1+microglia in Parkinson's Disease (PD) remains a topic of active investigation. Studies indicate that microglia, including Arg1+ subtypes, are influential in regulating neuroinflammation and immune responses in PD (Zhu *et al*., 2022). These microglia are involved in responses linked to neurodegeneration, such as inflammation and phagocytosis, which can either worsen or alleviate disease progression (Ho MS, 2019). Similarly, in Huntington's Disease (HD), the presence of Arg1+microglia are implicated in disease pathogenesis and advancement (Yang *et al*., 2017). Research suggests that microglial activation, including the involvement of Arg1+microglia, contributes to the observed neuroinflammatory processes in HD (Yang *et al*., 2017). Microglia, including Arg1+ subtypes, can adopt various activation states, such as the M1 phenotype and the M2 phenotype. In HD, an imbalance towards a predominantly pro-inflammatory state (M1) in microglial activation can worsen neuroinflammation and neuronal damage, thereby advancing disease progression (Yang *et al*., 2017; Saba *et al*., 2022). The presence of Arg1+microglia in HD may signify an effort by the brain to counteract pro-inflammatory responses and promote a more anti-inflammatory environment (Saba *et al*., 2022). More research is necessary to comprehensively grasp the precise role of Arg1+microglia in HD development and their effects on disease advancement, especially concerning their involvement in neuroinflammation, neuronal malfunction and neurodegeneration.

In conclusion, while Arginase 1 exhibits beneficial effects such as neuroprotection and anti-inflammatory properties in neurodegenerative disorders, its negative impacts like L-arginine depletion and potential neurotoxicity highlight the intricate balance that must be maintained for optimal neurological health. Developing precision-based therapies that target Arginase 1 to leverage its beneficial effects while minimizing its adverse outcomes may offer potential for novel treatments in neurodegenerative diseases.

NATURAL PRODUCTS TARGETING ARGINASE-1

Arginase 1 is a significant enzyme responsible for breaking down L-arginine and its excessive activation is associated with a variety of diseases such as cardiovascular disorders, cancer and neurodegenerative conditions (Li *et al*., 2022). Natural substances have been identified for their ability to influence Arginase 1 activity, offering potential therapeutic benefits. Compounds like Quercetin, quercitrin, isoquercitrin, taxifolin, rutin and quercetin-3-O-glucuronide have been found to inhibit

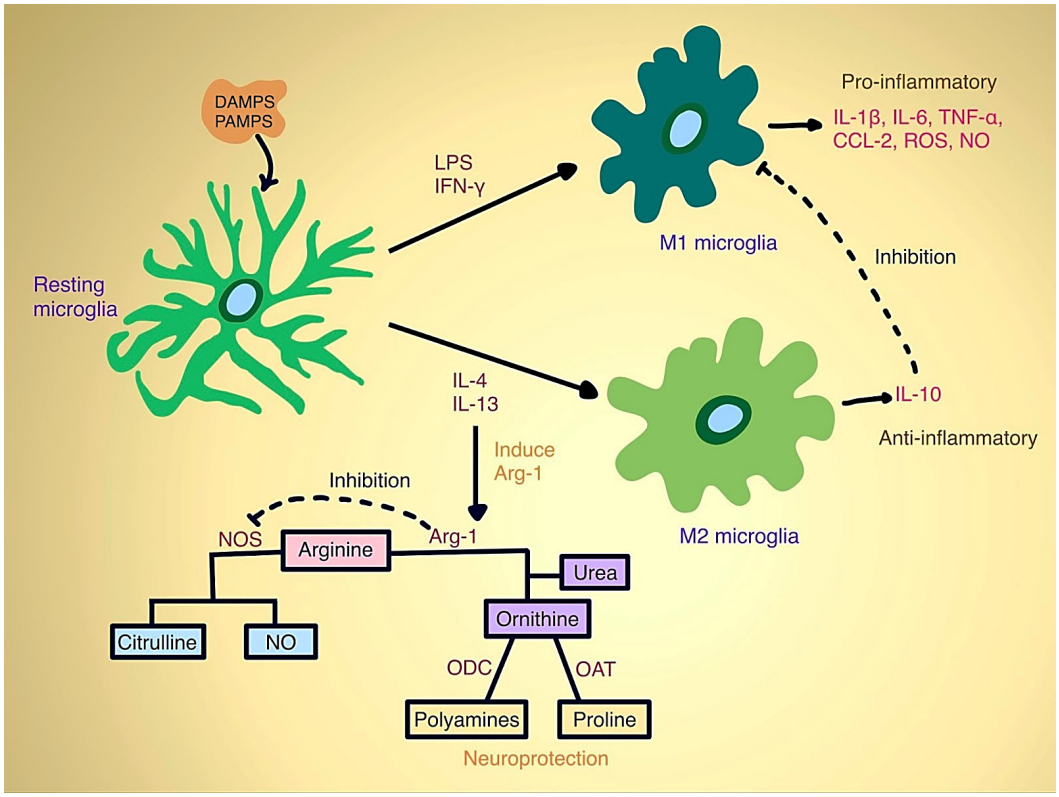

Figure 2: Based on the stimuli resting microglia is characterised into M1 and M2 phenotypes. Arginase-1 (Arg1) is activated in response to IL-4 or IL-13 and exerts anti-inflammatory effects by utilizing arginine, a common substrate, to suppress the production of Nitric Oxide (NO). Sustained high expression of Arg1 shifts arginine metabolism towards producing proline or polyamines, while concurrently reducing NO levels. This mechanism contributes to neuroprotection (Tang and Le, 2016). ODC, ornithine decarboxylase; OAT, ornithine aminotransferase.

Arginase 1, showing promise in treating diseases like cancer (Niu *et al*., 2022). Moreover, phenolic compounds like curcumin and resveratrol have shown potential in regulating Arginase 1 activity, suggesting their role in tumor immunotherapy and neural disease treatment by targeting this enzyme (Minozzo *et al*., 2018). Through Arginase 1 inhibition, these compounds help regulate L-arginine metabolism, crucial for various cellular functions and disease-related signalling pathways. L-arginine is influential and crucial in processes such as protein synthesis, cell signalling, immune response and vasodilation (Polis and Samson, 2018).

Resveratrol

Resveratrol (Figure 3a), commonly present in red grapes and berries, features a chemical structure comprising two aromatic rings linked by a carbon-carbon double bond (Duta-Bratu *et al*., 2023). Resveratrol inhibits arginase activity, which can have neuroprotective effects by regulating the metabolism of L-arginine (Yan *et al*., 2020). By inhibiting arginase, resveratrol may influence the production of urea and ornithine, affecting pathways involved in nitrogen disposal and polyamine synthesis. This modulation of arginase activity by resveratrol could impact neuronal function and survival, contributing to neuroprotection (Yan *et al*., 2020). Also, demonstrated neuroprotective effects and the ability to modulate microglial polarization. By interacting with Arginase-1, resveratrol can influence the balance between M1 and M2 phenotypes in microglia., contributing to anti-inflammatory responses (Yang *et al*., 2017).

Piceatannol

This is a derivative of resveratrol; piceatannol (Figure 3b) has a similar chemical structure to resveratrol but with additional hydroxyl groups (Piotrowska *et al*., 2012). Piceatannol, also exhibits inhibitory effects on arginase activity. By targeting arginase, piceatannol may influence the balance of L-arginine metabolism and the production of urea and ornithine (Bonnefont-Rousselot, 2016). These effects could contribute to neuroprotection by regulating pathways involved in cellular function and survival.

Epicatechin

Epicatechin (Figure 3c) is a flavonoid found in various plants like tea and cocoa. Its chemical structure includes two aromatic rings with hydroxyl groups (Eugene *et al*., 2022). Epicatechin acts as an uncompetitive arginase inhibitor, potentially impacting the enzymatic activity of Arginase-1 (Ortiz-Vilchis *et al*., 2018). By modulating arginase function, epicatechin may influence the availability of L-arginine for nitric oxide production and other cellular processes. This modulation could have neuroprotective effects by regulating nitric oxide levels and maintaining cellular homeostasis (Cater *et al*., 2021).

Curcumin

This is a phytochemical derived from turmeric and has a chemical structure with two aromatic rings connected by two α, β-unsaturated carbonyl groups (Hatamipour *et al*., 2018). Curcumin (Figure 3d) has been identified as a potent natural product with anti-inflammatory properties that can influence microglial polarization. It has been shown to target Arginase-1,

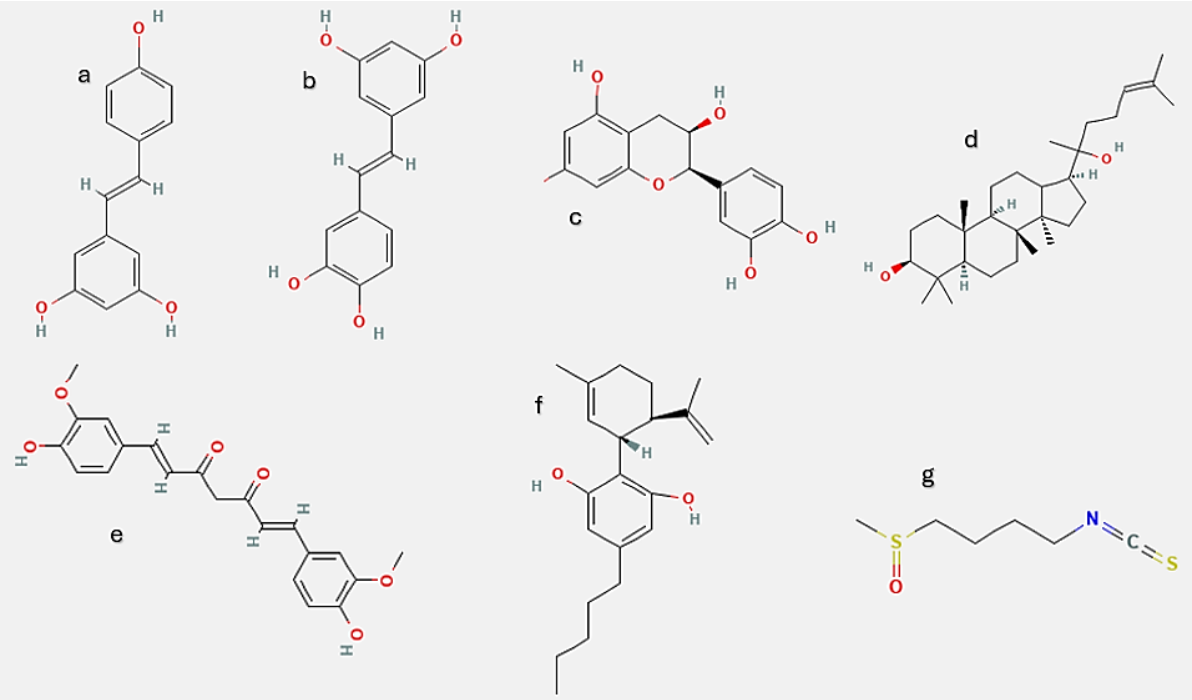

Figure 3: a- Resveratrol b- Piceatannol c- Epicatechin d- Curcumin e- Cannabidiol f- Ginsenosides g- Sulforaphane.

promoting the shift of microglia from the M1 phenotype to the M2 phenotype (Abdollahi *et al*., 2023).

Cannabidiol

Cannabidiol (Figure 3e) is a compound derived from the cannabis plant, which has a chemical structure with a resorcinol core and a monoterpene tail (Appendino *et al*., 2011). It has shown promise in regulating microglial polarization by targeting Arginase-1. Studies suggest that cannabidiol can promote the anti-inflammatory M2 phenotype in microglia, potentially influencing neuroinflammation in neurodegenerative diseases (Tao *et al*., 2016).

Ginsenosides

These bioactive compounds found in ginseng, have a complex chemical structure with multiple sugar moieties attached to a steroid-like core (Jee *et al*., 2014). Ginsenosides (Figure 3f) have been investigated for their immunomodulatory effects on microglia. By interacting with Arginase-1 and other proteins, ginsenosides can influence microglial polarization towards the anti-inflammatory M2 phenotype (Choi and Kim, 2023).

Flavonoids

Flavonoids are a diverse group of compounds with a common structure consisting of two aromatic rings connected by a three-carbon bridge (Khare *et al*., 2022). These compounds are recognized for their abilities as antioxidants and anti-inflammatory agents. Studies indicate that flavonoids can modulate microglial polarization by targeting Arginase-1 and promoting the shift towards the M2 phenotype, which is associated with reduced neuroinflammation (Da Silva *et al*., 2017).

Sulforaphane

Sulforaphane (Figure 3g) is found in cruciferous vegetables and has a chemical structure that includes a sulfinyl group attached to an isothiocyanate functional group (Mokhtari *et al*., 2018). It has been studied for its potential in neuroprotection. By interacting with Arginase-1 and other molecular targets, sulforaphane can influence microglial polarization towards the M2 phenotype, potentially mitigating neuroinflammation in neurodegenerative disorders (Darwish *et al*., 2023).

CHALLENGES AND FUTURE PROSPECTIVE

The use of natural products to target Arg1 for the treatment of neurodegenerative diseases presents a novel and promising approach. Bioinformatic and molecular studies allow us to identify natural products that can regulate Arg1 and L-arginine to treat neurodegenerative disorders. Through computational screening techniques, large databases of natural products can be screened to identify molecules that have the potential to regulate Arg1 or L-arginine metabolism. This approach allows for the rapid identification of promising candidates for further experimental validation. Bioinformatics tools can be used to predict potential targets of natural products based on their chemical structures and known biological activities. Identification of proteins like Arg1 that interact with L-arginine and play a role in neurodegenerative pathways. Molecular docking simulations can be utilised to predict binding affinities and interactions of natural products and binding sites of Arg1 and L-arginine. Following *in silico* studies, for further validation *in vitro* and *in vivo* studies can be conducted using cell culture techniques and mice models. By validating findings from bioinformatic analyses and molecular experiments through functional assays, biochemical assays and preclinical studies will be able to determine the efficacy and safety of identified natural products for targeting Arginase-1 in neurodegenerative diseases.

The bioavailability of natural products, especially when administered orally, can be a limiting factor in their efficacy. Ensuring adequate absorption, distribution and stability of these compounds in the body is essential for their therapeutic potential in neurodegenerative conditions. To enhance the bioavailability of natural products, various strategies can be employed. Formulation techniques such as encapsulation, complexation, or nano emulsion can improve stability and solubility, thereby enhancing absorption. Additionally, co-administration of absorption enhancers or inhibitors of metabolic enzymes can increase the uptake of natural compounds into the bloodstream. Blood-brain barrier permeability presents another challenge, as it restricts the passage of molecules into the brain. Strategies to enhance BBB permeability, such as using prodrugs or conjugates, can facilitate the delivery of natural products to the central nervous system. Moreover, ensuring the stability of natural compounds in systemic circulation is crucial for maintaining their efficacy. Metabolic enzymes in the liver and other tissues can metabolize or degrade these compounds, reducing their concentration and bioactivity. Structural modifications or the use of enzyme inhibitors can prolong the half-life of natural products and enhance their therapeutic potential.

CONCLUSION

In summary, the intricate relationship between arginase, nitric oxide and arginine influences immune responses, neuroinflammation and neurodegenerative processes. Understanding how these components interact can provide insights into potential therapeutic strategies for managing neuroinflammatory conditions and neurodegenerative diseases. The research on natural products targeting Arginase-1 for neurodegenerative diseases holds promise for the development of novel therapeutic interventions. Overcoming challenges related to toxicity, specificity, bioavailability and drug interactions is essential to harness the full therapeutic potential of natural products in targeting Arginase-1 for the treatment of neurodegenerative conditions.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

Arg1: Arginase 1; **CNS:** Central Nervous System; **BBB:** Blood Brain Barrier; **PAMPs:** Pathogen-Associated Molecular Patterns; **DAMPs:** Damage-Associated Molecular Patterns; **IFNγ:** Interferon-gamma; **LPS:** Lipopolysaccharide; **TNFα:** Tumor Necrosis Factor Alpha; **IL-6:** Interleukin-6; **IL-1β:** Interleukin-1β; **IL-4:** Interleukin-4; **IL-13:** Interleukin-13; **NO:** Nitric Oxide; **NOS:** Nitric Oxide Synthase; **ODC:** Ornithine Decarboxylase; **OAT:** Ornithine Aminotransferase.

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