Australian rainforest remedies: Scientists explore bioactive plant compounds as potential anti-neuroinflammatory agents

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Jul 9 2023

In a recent review published in the *International Journal of Molecular Sciences*, researchers provide an overview of bioactive plant compounds as potential anti-neuroinflammatory agents and the procedures involved in their development.

Study: From the Bush to the Brain: Preclinical Stages of Ethnobotanical Anti-Inflammatory and Neuroprotective Drug Discovery—An Australian Example.
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Harnessing the therapeutic potential of rainforests

Given their long geographical isolation from the world, the Australian rainforests provide a rich source of herbal remedies that have developed despite tremendous ecological challenges over the years. The rainforest is naturally rich

in secondary metabolic products that need further research and validation to be incorporated into disease management and improve human health.

Aboriginal communities in Australia provide valuable sources for identifying novel drug leads for treating various infectious and non-infectious diseases, including inflammation-related illnesses. These plants, such as *Melaleuca alternifoliavia*, *Eucalyptus*, *Angophora costata*, *Centipeda minima*, *Ipomoea pes-caprae*, *Tinospora smilacina*, *Ficus opposite*, *Passiflora foetida*, *Eremophila*, and *Dodonaea viscosa*, are known for their diverse flora and high biotic pressures.

The rainforests likely produce higher concentrations and varieties of pharmacologically active plants, thus making these regions a critical source of novel bioactive compounds. Understanding the complex chemical interactions between plants, animals, and microbes in the tropical rainforest is crucial to identify novel bioactive compounds.

The therapeutic potential of rainforest plants can be appreciated from past achievements, such as quinine used in malaria treatment, tubocurarine as a muscle relaxant, cocaine as a local anesthetic, and EBC-46 to destroy cancer cells.

Discovering novel nutraceuticals for neurodegenerative diseases

Neurodegenerative diseases are influenced by inflammatory neurotoxicity and microglial activation, which can be triggered at the central and local levels. Activated microglial cells secrete neurotoxic molecules like reactive oxygen species (ROS) and tumor necrosis factor-alpha (TNF-α) that damage neighboring neurons. Damage-associated molecular pattern molecules (DAMPs) that activate microglia are released by damaged neurons, which subsequently leads to additional microglial activation.

Chronic neuroinflammation-targeted treatments have been proposed as disease-modifying for a variety of neurodegenerative disorders, including Alzheimer's disease (AD). Cytokine-suppressing anti-inflammatory drugs (CSAIDs) and nutraceuticals may be better alternatives to conventional non-steroidal anti-inflammatory drugs (NSAIDs) for managing pain and inflammation.

NSAIDs are ineffective in neuroinflammatory disorders, as they do not interfere

with chemokine and cytokine production at therapeutic concentrations. Nutraceuticals, including apigenin, curcumin, epigallocatechin gallate, docosahexaenoic acid, resveratrol, and alpha-lipoic acid, possess anti-inflammatory properties and are regarded as CSAID prototypes. Animal studies have reported that apigenin and curcumin exert anti-inflammatory effects and penetrate the blood-brain barrier.

Curcumin, the primary curcuminoid in turmeric (*Curcuma longa*), inhibits interleukin-6 (IL-6), TNF-α, and nitric oxide (NO) production in microglia. Studies using glial fibrillary acidic protein (GFAP) and IL-6 murine models indicate that curcumin could reverse the detrimental effects of chronic glial activation during neuroinflammation and be used to treat neurodegenerative diseases. Despite its anti-inflammatory activity, curcumin has limited bioavailability and stability.

Traditional usage in medicine and ethnobotanical research has facilitated the identification of numerous bioactive plants. Subsequently, plant extracts are subjected to high-throughput biological screening and purification using high-performance liquid chromatography (HPLC).

X-ray crystallography, nuclear magnetic resonance (NMR) spectroscopy, and mass spectrometry are also used to identify the structure of the bioactive chemicals. Furthermore, the efficacy of bioactive chemicals is evaluated by *in vitro* and *in vivo* experiments that simulate the intricate interactions within the brain.

Cell-based screening assays for studying neuroinflammation

Macrophages are essential immune cells and play a crucial role in regulating lymphocyte activation and proliferation. In research, macrophage murine cell lines like RAW 264.7 and J774 provide a convenient *in vitro* model for drug screening, thereby reducing costs and time.

Macrophages are attracted to foreign substances through antibodies and play a protective role in destroying invaders through phagocytosis. Macrophages also produce cytokines, such as IL-3, IL-4, and IL-10, which induce proliferation and collagen production.

Microglia, immunocompetent cells of the central nervous system, play a key role in brain defenses by acting as dead cell scavengers and immune effector cells. These cells express pattern recognition receptors (PRRs) and toll-like

receptors (TLRs), thus impacting innate immunity.

One potent stimulus that activates microglia is lipopolysaccharide (LPS), the TLR-4 ligand, which is secreted by N11 and BV-2 microglial cells. Immortalized microglial cells eliminate the burden of primary cultures and provide robust *in vitro* models for studying brain inflammation and drug screening. Animal models of inflammation include rodent models of LPS-induced acute neuroinflammation and chronic inflammation models, such as immune-challenged-based, toxin-induced, and GFAP IL-6 transgenic models.

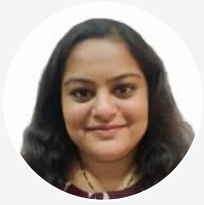
Future outlook

Based on the review findings, the Australian rainforest is enriched with therapeutic plants that have evolved despite environmental challenges. Previous studies have explored potent bioactive and anti-inflammatory chemicals derived from plants that have undergone structural identification, potency testing, neuroprotection, and validation in GFAP-IL6 murine models.

Further research is needed to evaluate plant-sourced bioactive compounds in murine neuroinflammation models before toxicology assessments and human studies can be initiated.

Journal reference:

- Kumar, P., Matthew, S., Gamage, R., *et al.* (2023). From the Bush to the Brain: Preclinical Stages of Ethnobotanical Anti-Inflammatory and Neuroprotective Drug Discovery—An Australian Example. *International Journal of Molecular Sciences 24*. doi:10.3390/ ijms241311086



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