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POTENTIAL OF BIOACTIVE COMPOUNDS FROM GAMBIER (UNCARIA GAMBIR ROXB.) IN MODULATING COGNITIVE FUNCTION: A SCOPING REVIEW

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ABSTRACT
Aging is a process of diminishing tissue capacity for self-repair and maintenance of normal structure and function, leading to vulnerability to injury and damage. The high incidence of neurodegenerative diseases coincides with increased life expectancy in the elderly. An unavoidable negative effect of neurodegenerative diseases is the potential to cause cognitive decline. Gambier (Uncaria gambir Roxb.), containing 90% catechin, is a traditional plant with potential to enhance cognitive function. This scoping review aims to map existing research on the potential of bioactive compounds from gambier in modulating cognitive function, based on research articles in journals from the last 10 years in the PubMed, PMC, Google Scholar, and Google Scholar databases (2014-2024). The research was conducted by collecting research data from the last 10 years, totaling 12 articles. Among these, 4 articles met the inclusion criteria, focusing on the potential of bioactive compounds from gambier in modulating cognitive function. The article screening was conducted systematically using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) as 1 a guideline, followed by screening based on inclusion and exclusion criteria. This scoping review found potential for bioactive compounds from gambier in modulating cognitive function, as evidenced by increased Montreal Cognitive Assessment (MoCA) scores, decreased levels of Beta Amyloid (Aβ), Microtubule-Associated Protein Tau (MAPT), Malondialdehyde (MDA) levels, and increased Brain-Derived Neurotrophic Factor (BDNF). The potential of catechin, the primary bioactive compound in gambier, which possesses antioxidant, anti-inflammatory, and neuroprotective effects, yields beneficial results in enhancing cognitive function in the elderly.

Keywords: cognitive function; gambier; neurodegenerative biomarker

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INTRODUCTION

Aging is a global phenomenon that carries significant consequences for public health. With increasing age, there is a decline in cognitive function that can affect the quality of life in the elderly. Cognitive impairment, ranging from mild memory loss to dementia, represents a major challenge in the elderly population (Baba, Inagaki, Nakagawa, Kaneko, *et al.*, 2021). Cognitive function is a complex function in the human brain involving memory (short-term or long-term), attention, planning, reasoning, and strategic thinking. Cognitive function declines with age (Baba, Inagaki, Nakagawa, Kaneko, et al., 2021). As life expectancy in the elderly increases, the health problems they face also become more complex, especially diseases related to neurodegeneration. Neuronal death in neurodegenerative diseases is caused by many factors, including aging, genetics, reactive oxygen species (ROS), synaptic injury, mitochondrial damage at the cellular level, protein misfolding and aggregation, and chronic inflammation (Afzal, et al., 2022).

The aging process creates an imbalance between oxidants and antioxidants. In the elderly, there is a decline in the body's natural antioxidant capacity, leading to the accumulation of free radicals in the brain. This triggers damage to nerve cell components, namely DNA. DNA damage can disrupt gene functions essential for nerve cell survival and function, such as changes in APP gene expression. Studies indicate that APP gene mutations affect γ-secretase enzymatic activity, leading to an increased ratio of Aβ40 to Aβ42 (Zhang, et al., 2022). Another nerve cell component affected is lipids. Lipid peroxidation triggers fat damage in cell membranes, which can disrupt nerve cell membrane integrity and synaptic function. Studies have shown a downregulation of BDNF in the brain, resulting in decreased conductivity of the nervous system (Nini, 2021). Free radicals also influence inflammation, mitochondrial damage, synaptic dysfunction, and abnormal protein accumulation in the brain, which will trigger cognitive decline.

The use of natural substances with neuroprotective properties is one exciting field of study. The plant known as gambler (Uncaria gambir Roxb.) has long been utilized in Southeast Asian traditional medicine. Bioactive substances with anti-inflammatory and antioxidant qualities, like tannins and catechins, are abundant in gambler. Given the important roles that inflammation and oxidative stress play in the pathophysiology of age-related cognitive decline, these characteristics are extremely pertinent to the maintenance of cognitive function.

Indonesia is the world's largest producer of gambier, meeting more than 80% of global demand. West Sumatra is one of the gambier-producing provinces in Indonesia, with 50 Kota Regency as its largest center (Ulya, et al., 2017; Rahmawati, et al., 2012). Extracts/resin from gambier leaves and twigs contain catechu tannic acid (tannin), catechin, pyrocatechol, fluorescein, waxes, and fatty oils, with the main component of gambier leaf extract being catechin (40-80%). Catechin is a polyphenol compound with antioxidant, anti-inflammatory, and neuroprotective effects (Baba, et al., 2020).

In vivo studies conducted on aging model female mice showed a decrease in Malondialdehyde (MDA) levels in the treatment group and an increase in BDNF expression in the treatment group administered gambier catechin (Sebayang, et al., 2020). Another in vivo study also demonstrated that administration of gambier leaf extract at a dose of 200 mg/kgbw in experimental animals was more effective in increasing sirtuin 3 expression (Sinaga, et al., 2020). Research (Rosalina, 2017) also showed that gambier catechin (*Uncaria gambir Roxb*.) was able to reduce 4-HNE levels in plasma, Aβ, and APP, and improve cognitive function in Alzheimer's model rats. Another study also demonstrated neurocognitive improvement, characterized by improved spatial memory and locomotor activity using the Y-maze, and decreased phosphorylated tau concentration in female AD model rats after administration of gambier catechin (Fasrini, et al., 2017). Another study in humans showed that gambier can improve attention and information processing speed.

Neuronal and synaptic dysfunction and loss in neurodegenerative diseases in the elderly will potentially increase with the growing elderly population. The objective of this study is to identify published research articles on the potential of bioactive compounds from gambier, with its main component catechin, in modulating cognitive function in the elderly. The findings are critically appraised and presented in terms of enhancing cognitive function in the elderly.

METHOD

This research employs a descriptive study design with an observational approach through a scoping review. The study aims to determine the potential of gambier in improving cognitive function. The research was conducted from January to December 2024. The study utilizes the

scoping review method. This research is a scoping review of experimental studies. The research follows the 5-step scoping review procedure according to the guidelines from Arskey and O'Malley in 2005 and The Joanna Briggs Institute Reviewer's Manual 2015: Methodology for JBI Scoping Review1. These steps include identifying the research question, identifying relevant literature, selecting literature, charting the data, and collating, summarizing, and reporting the results. All journals and articles were obtained from: PubMed, PMC, Google Scholar, Google Scholar, and Portal Garuda. After the article search, the article selection process was carried out. A total of 12 articles were found. The article screening was conducted systematically using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) as a guideline, followed by screening based on inclusion and exclusion criteria.

The inclusion criteria were: (1) articles discussing gambier catechin (*Uncaria gambir Roxb.)*, (2) articles discussing cognitive function in the elderly and molecular markers of cognitive impairment, (3) articles published within the last 10 years. The exclusion criteria were: (1) articles without full-text access, (2) articles in the form of literature reviews. Subsequently, the first study selection process was conducted by screening articles, where titles and abstracts were read to determine the exclusion of articles that were not relevant to this study. The remaining articles that met the inclusion criteria were then reviewed in their entirety. Articles deemed eligible and suitable were then included in the data extraction.

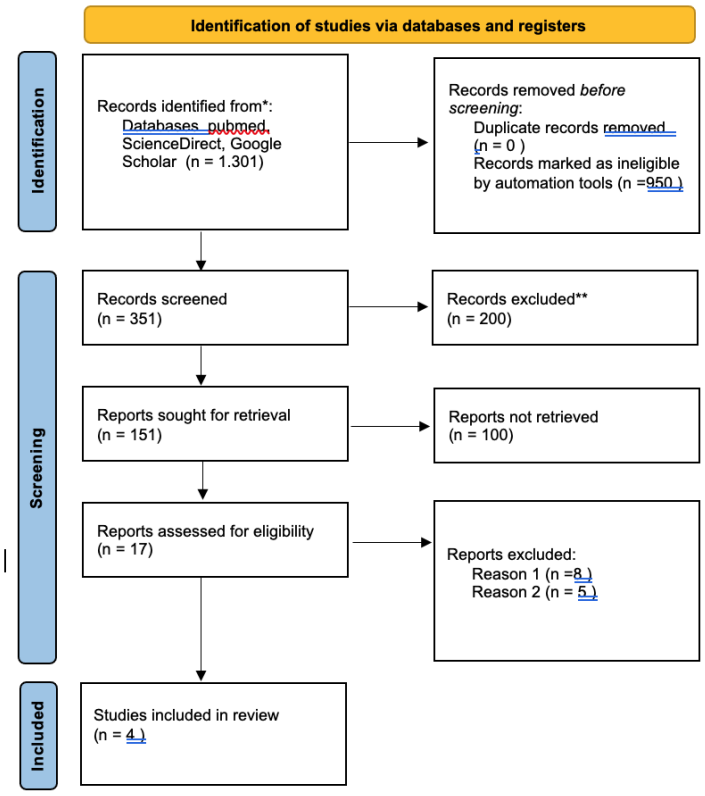

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR)

RESULT

An extensive literature search successfully identified 1301 potentially relevant records. The identification continued using tools available in PubMed, ScienceDirect, and Google Scholar, resulting in the removal of 950 irrelevant articles. Subsequently, 351 articles were read to assess their

completeness according to the inclusion and exclusion criteria, resulting in 4 relevant articles for the review process.

Table 2.
Article Analisys

Reference	Literature	Method	Results
Linda Rosalina dkk, 2017	Inhibition of Free Radicals and Improvement of Cognitive Function in Alzheimer's Model Rats by Gambier Catechin	- Experimental Study, - Desain post test only randomized control group - Invivo-	- The administration of gambier catechin at doses of 20, 40, and 60 mg/200mg body weight significantly influenced the 4-HNE plasma levels in Alzheimer's model rats
Ulya Uti Fasrini dkk, 2017	Effect of Gambier (*Uncaria gambir/Hunter Roxb*.) on Locomotor and Neurocognitive Activity in Female Alzheimer's Model Rats	- Studi eksperimental - Desain: post treatment only - A sample of 25 female Alzheimer's model rats, 12 weeks old, with confirmed cognitive impairment.	- There was a significant difference in the AC3 group (69% and 82%) after 4 weeks of oral administration of gambier catechin at doses of 40 and 60 mg/200mg body weight in rats
Inda Meirani H sinaga dkk, 2020	Effect of Gambier Leaf Extract (*Uncaria gambir Roxb*.) on Oxidative Stress Levels and Sirtuin 3 Expression in the Hippocampus of D-Galactose-Induced Aging Model Female Mice	- Studi eksperimen - Desain: post test only control grup - A sample of 24 female mice, 12 weeks old	- Oral administration of gambier leaf extract at a dose of 200 mg/kg body weight showed an increase in SIRT3 expression in the intervention group - Oral administration of gambier leaf extract at a dose of 200 mg/kg body weight is an effective dose to improve memory in mice ($p < 0.05$)
Julendairianti dkk, 2020	Effect of Gambier Leaf Extract (*Uncaria gambir Roxb*.) on Oxidative Stress Levels and BDNF Gene Expression in the Hippocampus of D-Galactose-Induced Aging Model Female Mice	- Studi eksperimen - Desain: post test only control grup - A sample of 24 female mice, 12 weeks old	- MDA was lower in the K2 group than in the control group, however the difference was not statistically significant. - BDNF Gene Expression Was Higher in the K2 Group Than in the Control Group

DISCUSSION

Composition of gambier

A shrub in the Rubiaceae (coffee) family, the gambler (Uncaria gambir Roxb.) resembles the bougainvillea tree in that it is woody and climbs. Gambier can grow to a height of one to three meters. with a pale brown tint, sympodial branching, and an upright, spherical stem. Its solitary, opposite, oblong leaves are green in color, 8–13 cm long, and 4–7 cm wide. They have serrated edges, a rounded base, and a pointy tip. The compound flowers, which are 5 cm long and have five oval-shaped purple petals, resemble bells on the leaf axils. With a diameter of up to 2 cm, the fruit resembles a pseudo-pod and is packed with tiny, 1-2 mm seeds. (Fasrini, et al., 2017).

Extracts/resin from gambier leaves and twigs contain catechu tannic acid (tannin), catechin, pyrocatechol, fluorescein, waxes, and fatty oils. The main component of gambier is catechin, with the composition (7-33%) being catechinic acid or cathecu acid, catechin tannate (20-50%), and pyrocatechol (20-30%). Differences in catechin levels in gambier are influenced by the age of the gambier leaves; young gambier has a higher extract yield compared to old gambier leaves (Mahendar and Minda, 2022). The total catechin content of gambier leaf extract in Indonesia varies widely, ranging from 40-80%. In Indonesia, gambier leaf extract's total catechin content varies greatly, ranging from 40 to 80%. According to the Indonesian National Standard (SNI), gambier (SNI 01-3391-2000) has a 40–60% catechin content overall. (Anggraini, et al., 2011; Fasrini, et al., 2017).

The gambier plant's shoots and leaves are rich in catechins, sometimes referred to as flavan-3-ols, which make up 70–80% of the polyphenol chemicals in the Rubiaceae family. Catechin (C), epicatechin (EC), epicatechin gallate (ECG), epigallocatechin (EGC), and epigallocatechin gallate (EGCG) are the constituents of catechins. Because of the hydroxyl groups in their structure, catechins have strong antioxidant qualities that allow them to scavenge reactive oxygen species (ROS), such as superoxide radicals, nitric acid, and hydroxyl radicals, which contribute to neurodegeneration and cancer (Ortega et al., 2022). Gambier includes catechu tannic acid (tannin) in addition to catechins. Tannins are antioxidants and astringents. The astringent flavor of gambier is a result of tannins' ability to bind proteins. They can also neutralize free radicals because of their antioxidant qualities.

Potential of Gambier Bioactive Compounds (Catechin) in Enhancing Cognitive Function

The MoCA score's Indonesian version was used to measure cognitive function. The MoCA assessment's measuring findings are separated into two groups: impaired (score <26) and normal (scoring 26 to 30). (Dautzenberg, 2020). According to research, gambier's catechins are a class of naturally occurring antioxidants that guard against brain cell death by scavenging reactive oxygen species (ROS), which helps to prevent and delay dementia. (Antony, et al., 2018). Catechin also has the capacity to interact with intracellular signaling pathways in neurons, which affect neurodegeneration and neuroinflammation, processes involved in memory, learning, and cognitive function.

Previous research has shown that the administration of gambier catechin at doses of 40 and 60 mg/200g body weight for 4 weeks improved spatial memory and locomotor activity using the Y-maze in female Alzheimer's model rats (Fasrini, et al., 2017). Several studies suggest that catechin consumption in certain amounts and over a specific period can enhance cognitive function. Clinical research in the elderly has shown an increase in MoCA scores in the language domain in active female subjects compared to female placebo subjects after 12 weeks of matcha powder consumption (Sakurai, et al., 2020).

According to another clinical study, following 12 weeks of treatment with a catechin dose of 336.4 mg/day, the Japanese version of the Mini-Mental State Examination (MMSE-J) demonstrated that the catechin in green tea improved cognitive function. (Baba, et al., 2020). These literature findings demonstrate that catechin has significant potential in enhancing cognitive function in the elderly.

Potential of Gambier Bioactive Compounds in Reducing Neurodegenerative Biomarkers

Catechin is thought to lessen oxidative stress because of its anti-inflammatory, antioxidant, and neuroprotective qualities as well as its capacity to scavenge radicals. (Baba, et al., 2020; Polito, et al., 2018). Numerous pathophysiological factors, including smoking and metabolic disorders, can cause cellular-level oxidative stress in the aged. The first sign of oxidative stress is mitochondrial malfunction, which raises glutamate receptor (NMDA) levels. The neurotrophic factor BDNF is also impacted by oxidative stress in the cortex and hippocampus and inflammation in the central nervous system. The synthesis and consolidation of new memories are aided by BDNF.

In vivo research (Rosalina, et al., 2017) has demonstrated that gambier catechin can enhance cognitive performance in Alzheimer's model rats and lower plasma levels of 4-HNE, BACE 1, and Aβ. Additional findings indicate that when gambier leaf extract is administered to female mice in a D-galactose-induced aging scenario, oxidative stress levels decrease. (Sinaga, et al., 2020). Research (Sebayang, et al., 2020) In the hippocampus of female mice with a D-galactose-induced aging model, the effects of gambier leaf extract on oxidative stress levels and Brain-Derived Neurotrophic factor (BDNF) expression revealed that when gambier leaf extract was administered at a dose of 200 mg/kg body weight, MDA levels were lower in the treatment group than in the control group, and BDNF expression was higher in the treatment group. This suggests that catechin suppresses cognitive decline by preventing the buildup of oxidative damage to DNA in the brain.

Through its immunomodulatory properties, catechin also acts as an anti-inflammatory drug by regulating neuroinflammation, which is typified by microglial activation (Polito et al., 2018; Zhang et al., 2022). In APP transgenic mice, four months of EGCG ingestion decreased hippocampal amyloid plaques and inhibited microglial activation, as demonstrated by increased levels of the anti-inflammatory cytokine IL-10 and decreased levels of IL-1β. (Afzal, et al., 2022). This suggests that catechin can protect neurons by changing microglial activity and lowering the synthesis of inflammatory mediators via the NF-κB, Nrf2, and TLR4/NF-κB pathways. Iron buildup in the brain causes toxic Aβ aggregates in elderly people with neurodegenerative disorders. Investigate (Afzal, et al., 2022) implies that EGCG may have an impact on Aβ levels by preventing hyperphosphorylated tau from aggregating, degrading Aβ plaques, or blocking APP translation by lowering labile Fe2+. Additionally, catechin reduces BAX, caspase-3, Bad, and poly(ADP-ribose) polymerase (PARP) through protein kinase C signaling, exhibiting neuroprotective properties.

Alzheimer's dementia is thought to be largely caused by inflammation, oxidative stress, and the MAPT gene's hyperphosphorylation of tau protein and the APP gene's excessive Aβ accumulation. By increasing antioxidant activity and reducing oxidative stress, inflammation, Aβ aggregation action, and anticholinesterase activity, catechin exerts neuroprotective effects (Afzal, et al., 2022; Zhang, et al., 2022).

A clinical trial of catechin in green tea was conducted in Japan. This study demonstrated that the consumption of 1 catechin capsule daily at a single dose of 336.4 mg catechin for 12 weeks had beneficial effects on working memory in the elderly, as assessed through cognitive tests with Cognitrax, MMSE, and blood biomarkers Aβ (40 and 42), BDNF, APP770, and

sAPPα (Baba, et al., 2020; Baba, Kaneko, et al., 2021). In the brains of APP mice, similar studies also found that oral administration of epigallocatechin-3-gallate (EGCG) at a dose of 50 mg/kg for four months significantly increased dendritic integrity and synaptic protein expression levels. Additionally, EGCG demonstrated anti-inflammatory effects by decreasing proinflammatory cytokines (IL-1), increasing anti-inflammatory cytokines (IL-10 and IL-13), and decreasing microglial activation. (Baba, et al., 2020).

The process of nervous system repair in neurodegeneration after catechin consumption occurs through several mechanisms of action, including free radical neutralization, its role as an antioxidant effect, modulation of inflammatory signals through increased anti-inflammatory cytokines such as IL-10 and TGF-beta, its role in nerve cell protection where catechin can influence BDNF expression, inhibit enzyme activity, effects on aggregated proteins by inhibiting the formation and aggregation of toxic proteins such as Aβ and tau, play a role in nerve cell regeneration, mitochondrial protection, and effects on glial tissue and increased blood flow (Bao, et al., 2020).

A study (Zhang, et al., 2022) investigating the association between green tea consumption and cognitive function, as well as blood biomarkers, in middle-aged and elderly individuals in China, revealed that the group consuming tea exhibited higher MoCA scores (P=0.000). Regarding oxidative stress markers, the tea-consuming group demonstrated lower serum MDA levels and higher SOD and GPx levels. Additionally, Alzheimer's Disease (AD) markers, including MAPT gene, Aβ42, and total Aβ levels, were lower in the green tea consumption group. It can be concluded that regular green tea consumption is associated with enhanced cognitive function in the elderly, particularly in memory and executive functions. The neuroprotective effects attributed to catechins may offer beneficial outcomes for elderly individuals in their 60s, a critical period when age-related brain changes begin to manifest. The neuroprotective mechanisms of catechins in the nervous system involve slowing down or preventing the accumulation of damage, reducing the risk of neurodegeneration, enhancing and maintaining synaptic plasticity, and promoting antioxidant and anti-inflammatory responses (Zhang, et al., 2022)."

Future Research Plan

Research on the potential of gambier bioactive compounds to improve cognitive function holds significant promise for benefiting public health. The impact on cognitive function has been demonstrated by improved cognitive performance after intervention in animal models that have been studied both in vitro and in vivo using biomarkers of cognitive function. Clinical trials are still needed to determine the optimal amount of gambier catechin that can be administered to the elderly with minimal side effects. Research can employ a variety of biomarkers of cognitive loss in the elderly, including as APP, Aβ, BDNF, oxidative stress indicators, and inflammatory markers. The quality of life for older adults will be significantly impacted by future research on catechin's use as a neuroprotective agent in neurodegenerative diseases, particularly dementia.

CONCLUSION

This review shows that gambier catechin contributes significantly to the speed at which cognitive function improves. Four research that documented how gambier catechin's anti-inflammatory, antioxidant, and neurotrophic qualities helped experimental animals' cognitive function improve more quickly lend credence to this.

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