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Catechin-Rich Gambir (*Uncaria gambir Roxb.*) as a Nutraceutical Agent: Modulation of IL-10 Gene Expression and Cognitive Function in Elderly

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Abstract

Aging is associated with increased oxidative stress and chronic inflammation, which contribute to cognitive decline. Modulation of anti-inflammatory pathways, particularly through interleukin-10 (IL-10), may offer a neuroprotective strategy. Catechins, polyphenolic compounds with antioxidant and anti-inflammatory properties, are abundant in Uncaria gambir Roxb., an Indonesian plant with high catechin content. This study aimed to evaluate the effects of catechin-rich gambir supplementation on cognitive function and IL-10 gene expression in older adults. A randomized, double-blind, placebo-controlled trial was conducted involving 58 participants aged ≥60 years with mild cognitive impairment (MoCA-Ina scores 20–25). Participants received either 224 mg/day of catechin or placebo for 12 weeks. Cognitive function was assessed using the MoCA-Ina, and IL-10 gene expression was measured using quantitative real-time PCR (qRT-PCR). Catechin supplementation significantly improved cognitive function compared to placebo ($p < 0.001$) and increased IL-10 gene expression after 12 weeks ($p < 0.001$). These findings suggest that gambir-derived catechins may contribute to cognitive improvement through modulation of anti-inflammatory pathways. However, further studies are required to confirm long-term effects and clinical applicability.

Keywords: *Catechin; Uncaria gambir; Cognitive function; IL-10 gene expression; Neuroinflammation.*

Introduction

Aging is a biological process characterized by progressive physiological decline, particularly in brain function, which may lead to neurodegenerative diseases such as Alzheimer's disease [1,2]. Age-related cognitive impairment is strongly associated with increased oxidative stress and chronic neuroinflammation, driven by an imbalance between pro- and anti-inflammatory mediators. Reduced expression of key anti-inflammatory cytokines, such as interleukin-10 (IL-10), contributes to sustained neuroinflammation and neuronal damage [3,4].

Globally, population aging is increasing rapidly, accompanied by a rising prevalence of cognitive impairment and dementia [2,5]. This trend highlights the urgent need for effective preventive strategies targeting age-related neurodegeneration [6]. In recent years, natural bioactive compounds have gained attention as potential therapeutic agents due to their safety profile and biological activity [7,8].

Catechins are polyphenolic flavonoids with strong antioxidant and anti-inflammatory properties [9]. Their chemical structure, characterized by aromatic rings and multiple hydroxyl groups, enables them to neutralize reactive oxygen species (ROS), inhibit lipid peroxidation, and regulate signaling pathways involved in oxidative stress and inflammation [10–13].

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Uncaria gambir Roxb. (gambir) is a well-known natural source of catechins, with purified extracts containing up to ≥90% catechin, which is substantially higher than that found in green tea [14,15]. This high catechin content provides a strong pharmacological basis for its potential neuroprotective effects. In addition, the use of a locally abundant Indonesian resource highlights the potential for developing sustainable and region-specific nutraceutical interventions.

Mechanistically, catechins modulate key inflammatory pathways, including inhibition of nuclear factor kappa B (NF-κB), which regulates the expression of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 [16,17]. In parallel, catechins enhance anti-inflammatory responses by upregulating IL-10, thereby promoting neuroprotection and maintaining neuroimmune homeostasis [18].

Although previous studies have demonstrated the cognitive benefits of catechin supplementation, most have focused on green tea-derived catechins, and evidence regarding gambir-derived catechins remains limited [19,20]. Furthermore, the role of catechins in modulating IL-10 gene expression in relation to cognitive function in older adults has not been well established.

Therefore, this study aimed to evaluate the effects of catechin-rich gambir supplementation on cognitive function and IL-10 gene expression in older adults. Unlike previous studies primarily focusing on green tea catechins, the present study uniquely investigates high-purity gambir-derived catechins (≥90%) and their immunomodulatory effects through IL-10 gene expression, providing novel insights into nutraceutical strategies for cognitive aging.

Experimental

Equipment

The equipment employed for the experiment comprised of clinical testing devices as well as those for the molecular testing procedures. The MoCA-Ina Standardized Questionnaire was applied in the determination of cognitive functions within the population under study. Molecular testing was done through the isolation and analysis of gene expressions by employing the following apparatus: a refrigerated centrifuge, vortex mixer, micropipettes (0.1–1000 μL range), and biosafety cabinet. The concentration and purity were determined by the UV–Vis spectrophotometer and the complementary DNA was prepared using the thermal cycler. Quantitative real-time PCR (qRT-PCR) was performed using the qRT-PCR system to determine the expression levels of the interleukin-10 gene. The laboratory equipment used during the procedure included: the microcentrifuge, tube homogenizer, and cold storage units (−20°C and −80°C freezers). Calibration of all the instruments was done before the experiments commenced.

Materials

Purified gambir extract containing ≥90% (+)-catechin content was obtained from PT. Andalas Sitawa Fitolab (Indonesia) no. 01/PE-FP/2020. Such purity of catechins was chosen to ensure uniformity of the active compound and to highlight its role as an underlying compound in generating biological responses. Corn starch (amylum) was employed as a placebo. The active substance and placebo were encapsulated in identical hard gelatin capsules (No. 1) to ensure blinding. Primer for gene analysis of IL-10 was bought from Thermo Fisher Scientific (USA). All reagents used for isolating and analyzing RNA, including TRIzol® reagent, had the analytical purity.

Participants

For the experiment, elderly individuals residing in communities aged 60-90 years were recruited. Of all initial screened candidates (n=99), only 64 participants fulfilled all inclusion criteria. For the study, the minimal sample size is set at 58 individuals, which were subsequently allocated to two equally sized groups (n=29 each). Criteria for inclusion were as follows: (1) MoCA-Ina test result between 20 and 25 points; (2) agreement to take one capsule per day for 12 weeks; and (3) living in the same study area throughout the period of intervention. Criteria for exclusion were as follows: (1) Geriatric Depression Scale (GDS) score higher than 2 points; (2) presence of any neurodegenerative diseases (stroke, Parkinson's disease, epilepsy, brain injuries, etc.); and (3) taking medications that affect cognitive processes.

Intervention and Data Collection

Participants in the intervention group consumed 224 mg/day of catechin in the form of Uncaria gambir Roxb. orally once a day in the morning, two hours after breakfast, over a period of 12 weeks. For members of the placebo group, they received the same amount of a placebo that contained 224 mg of corn starch in a similar condition. Members in both groups were observed throughout the study to monitor adherence and to detect any side effect or use of concomitant drugs.

Assessment of Cognitive Function

Cognitive functioning test was done using the Indonesia version of Montreal Cognitive Assessment (MoCA-Ina). Pre-intervention baseline measures were taken three days before the start of intervention while the post-intervention assessment was performed after 12 weeks.

Methods

Blood Sampling and IL-10 Gene Expression Analysis

RNA Isolation

Total RNA isolation was done using TRIzol® following the manufacture's instruction. Samples were first homogenized and mixed with chloroform then subjected to centrifugation. The aqueous layer was recovered and RNA was precipitated using isopropanol. Ethanol was added to wash the RNA pellet which was later air dried and dissolved in RNase free water. Concentration of RNA was quantified then diluted to obtain 1000 ng/mL concentration.

cDNA Synthesis

The reverse transcription kit (Thermo Fisher Scientific, Lithuania) was used for cDNA synthesis. The mixture used in this experiment contained total RNA, reverse transcription buffer, oligo(dT) primers, dNTPs, DTT and reverse transcriptase. The final volume for RT reaction was 20 µl. The RT reaction was carried out at 52°C for 50 min.

Real-Time PCR (RT-PCR)

Real-time PCR was used to assess the IL-10 gene expression through the use of gene specific primers:

Forward primer: 5′-TGGCCCAGAAAATCAAGGAGC-3′

Reverse primer: 5′-CAGCAGACTCAATACACACT-3′

PCR amplification was repeated for 40 cycles using optimal temperature settings. The relative IL-10 gene expression was calculated using the comparative Ct ($2^{-\Delta\Delta Ct}$) technique.

Statistical Analysis

Shapiro-Wilk test was used for data normality testing, whereas Levene's test was used for homogeneity of variance testing. Data on IL-10 gene expression had normal distribution, hence the need to apply the independent t-test for further analysis. On the other hand, MoCA-Ina scores had failed the assumption of normal distribution, therefore subjected to the Mann–Whitney U test. All statistical tests were done using IBM SPSS Statistics software ver. 26. Significance level of $p < 0.05$ was adopted for significance testing.

Ethical Approval

This study has been approved by the Ethics Committee of the Faculty of Medicine, Universitas Andalas, Indonesia (Approval No: 115/UN.16.2/KEP-FK/2024). Procedures used in this study are in line with the principles outlined in the Declaration of Helsinki. Informed consents were signed by all subjects.

Results and Discussion

Participant Characteristics

A total of 58 aged individuals participated in this research, with 29 participants receiving the intervention (catechin) treatment and 29 forming the control group (placebo). Baseline characteristics of the participants will be given below to ensure that all the groups under study were comparable [22].

Sex Distribution

Sex distribution of the participants shows that there was a higher percentage of females in each group than males. While females made up 75.9% of the catechin group, they made up 55.2% of the placebo group, while males made up 24.1% and 44.8% respectively. Hence, the percentage of females was higher than that of males [23].

Age Distribution

The average age of participants in the catechin group was 66.51 ± 4.4 years, while that of placebo group members was 67.75 ± 5.4 years. It should be noted that there was similarity in age distributions among the two groups; aged participants ranged from 60 to 79 years in the catechin group, while the placebo group ranged from 60 to 81 years [24].

Occupational and Clinical Characteristics

Most participants were categorized as housewives (IRT), with a distribution of 62.1% and 48.3% in the catechin and placebo groups, respectively. Other job categories included retirees, private employees, and small traders. With respect to medical history, the highest prevalence of disease was found in the hypertensive patients, which constituted 37.9% of those in the catechin group and 41.7% in the placebo group. There were more individuals who were healthy in the placebo group (48.3%). It can be noted that the baseline characteristics are fairly similar for both groups before the intervention, hence it may be assumed that any changes post-intervention can be attributed to the intervention itself [25].

Effect of Catechin Supplementation on Cognitive Function

The cognitive ability of the subjects was determined using the MoCA-Ina (Montreal Cognitive Assessment – Indonesian version) before and after the intervention period, which lasted for 12 weeks [26], [27]. The results are provided in **Table 2** below.

Table 1. Baseline Demographic and Clinical Characteristics of Participants

Variable	Catechin	Placebo
Age (years)	66.51 ± 4.40	67.75 ± 5.40
Sex		
Male	7 (24.1%)	13 (44.8%)
Female	22 (75.9%)	16 (55.2%)
Occupation		
Housewife	18 (62.1%)	14 (48.3%)
Private sector	1 (3.4%)	4 (13.8%)
Trader	1 (3.4%)	2 (6.9%)
Retired	9 (31.0%)	7 (24.1%)
Others	0	2 (6.9%)
Medical history		
Healthy	8 (27.6%)	14 (48.3%)
Hypertension	11 (37.9%)	4 (13.8%)
Hyperuricemia	3 (10.3%)	6 (20.7%)
Diabetes mellitus	2 (6.9%)	2 (6.9%)
Others	5 (17.2%)	3 (10.3%)

Table 2. Changes in Cognitive Function Assessed by MoCA-Ina Before and After 12 Weeks of Intervention

Group	Pre (Median, Min-Max)	Post (Median, Min-Max)	p-value (between groups)
Catechin	21 (20-25)	25 (16-29)	< 0.001
Placebo	20 (20-24)	20 (18-28)	

Table 3. Changes in IL-10 Gene Expression Before and After 12 Weeks of Catechin Supplementation

Group	Pre (Median, Min-Max)	Post (Median, Min-Max)	p-value (between groups)
Catechin	1.39 (1.06-1.95)	2.92 ± 0.49	< 0.001
Placebo	1.56 (1.05–1.87)	2.20 ± 0.45	

In the baseline stage, the median MoCA-Ina score of the catechin group was 21 (range: 20–25), while that of the placebo group was 20 (range: 20–24). Based on the Mann-Whitney U test performed, the results revealed a significant difference between both groups at the baseline level (p = 0.01). Post-intervention assessment for the catechin and placebo groups, respectively, revealed a median score of 25 (range: 16–29) and 20 (range: 18–28), which is indicative of considerable improvement in the cognitive performance of the former group compared to the latter. In fact, there was a statistically significant difference between both groups after the intervention (p < 0.001). The within-group analysis based on the Wilcoxon signed-rank test demonstrated that the supplementation with catechin had led to an increase in MoCA-Ina scores (p < 0.001). No such effect was seen in the placebo group (p = 0.395). Conclusively, the administration of catechin extracted from Uncaria gambir Roxb. on a daily basis over a period of 12 weeks improved cognitive function [19].

Effect of Catechin Supplementation on IL-10 Gene Expression

The effect of catechin supplementation on IL-10 gene expression was evaluated using quantitative real-time PCR (qRT-PCR) before and after the 12-week intervention. Prior to the intervention, IL-10 gene expression levels were comparable between the catechin and placebo groups (p = 0.229), indicating no significant baseline difference. Following the intervention, IL-10 gene expression increased significantly in the catechin group compared to the placebo group (p < 0.001). Within-group analysis demonstrated a significant increase in IL-10 gene expression in both groups (p < 0.001); however, the magnitude of increase was substantially greater in the catechin group [18]. This finding suggests that catechin supplementation may enhance anti-inflammatory responses, as reflected by the upregulation of IL-10 expression. These results support the potential role of catechin derived from *Uncaria gambir* Roxb. in modulating anti-inflammatory pathways, although the underlying molecular mechanisms were not directly examined in this study.

This study demonstrated that daily supplementation with catechin derived from *Uncaria gambir* Roxb. for 12 weeks was associated with improvements in cognitive function and increased IL-10 gene expression in older adults. These findings suggest a dual role of catechin in enhancing cognitive performance while modulating anti-inflammatory responses [20].

The observed improvement in MoCA-Ina scores in the catechin group indicates a beneficial effect on global cognitive function. Notably, cognitive domains that are particularly vulnerable to age-related decline—such as memory, executive function, and attention—appeared to improve following supplementation. In contrast, no significant changes were observed in the placebo

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group, supporting the specificity of the catechin intervention [28], [29].

In addition, the significant upregulation of IL-10 gene expression in the catechin group suggests activation of anti-inflammatory pathways [30], [31]. IL-10 is a key immunoregulatory cytokine that suppresses pro-inflammatory cytokine production and inhibits excessive microglial activation, thereby supporting neuronal survival and maintaining neuroimmune homeostasis. The increase in IL-10 gene expression observed in this study indicates that catechin may modulate inflammatory responses implicated in cognitive decline [28], [29].

From a chemical perspective, the biological activity of catechins is closely related to their molecular structure, particularly the presence of multiple hydroxyl groups that contribute to their antioxidant capacity through the scavenging of reactive oxygen species (ROS) and reduction of oxidative stress [13]. Furthermore, catechins have been shown to inhibit the activation of nuclear factor kappa B (NF-κB), a transcription factor that regulates the expression of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 [34], [35]. Inhibition of this pathway may indirectly enhance anti-inflammatory responses, including IL-10 expression. The ability of catechins to cross the blood–brain barrier, as supported by previous pharmacokinetic studies, reinforces their potential for direct neuroprotective effects within the central nervous system. In addition, the reduction of peripheral inflammation may indirectly limit the infiltration of pro-inflammatory cytokines into the brain through a compromised blood–brain barrier, a condition commonly associated with aging [35]. This dual central–peripheral mechanism highlights the broad neuroprotective potential of catechins.

The upregulation of IL-10 gene expression observed in this study may reflect a shift toward an anti-inflammatory physiological state, which could help mitigate chronic inflammation associated with aging [36]. Chronic inflammation is a well-established contributor to neurodegeneration and cognitive impairment. Additionally, previous studies have reported that catechins can cross the blood–brain barrier, suggesting both systemic and central neuroprotective effects [37].

The results of this study are aligned with the literature, which supports the positive impact of catechin-enriched products, especially green tea, on cognitive function among the aged population [38], [39]. Earlier randomized control trials have revealed that catechin intake has led to better memory, concentration, and executive functioning skills, providing substantial proof regarding the neuroprotective effect of polyphenols [29]. Nevertheless, the main strength of using Uncaria gambir Roxb., compared to other known sources like green tea, lies in its extremely high catechin concentration, which can even reach 90% [40]. Such an increased level may increase the biological effectiveness of Uncaria gambir Roxb., as evident from the significant changes seen in the results. Furthermore, this study has also contributed to the literature by incorporating gene expression analysis along with the clinical evaluation of cognitive function.

A limitation of this experiment is that there was a significant difference in cognitive score at baseline in both groups. In this case, randomization may not guarantee uniformity in the initial value due to the relatively low sample size. Nonetheless, the significant effect produced by catechins in improving cognitive function shows that the impact of taking catechins is significant. In addition, an important finding from this study is the increased IL-10 gene expression in both groups. It may result from the physiological changes, life-style changes, and the placebo effect in both experimental groups [41]. Nonetheless, the increase in IL-10 in the catechin group is significantly higher than that in the control group; therefore, it is indicative of the effect of catechin supplementation. Furthermore, this study has a relatively short period (12 weeks). Further studies should address the long-term impacts of taking catechins.

Findings from this study have shown that the catechins in gambir have great potential as a locally produced nutraceutical to promote brain health during aging. Being one of the main producers of gambir in the world, there could be some health and economic advantage gained from the production of such functional materials based on catechin. In terms of scientific significance, this study adds to the understanding of the role of polyphenols in neuroinflammatory responses via an IL-10 pathway mechanism [18]. This integration of chemistry and biology is a significant addition to the study of functional biomaterials and nutraceutical science.

Conclusions

This study demonstrates that supplementation with catechin derived from *Uncaria gambir* Roxb. is associated with improvements in cognitive function and increased IL-10 gene expression in older adults with mild cognitive impairment. These findings suggest a potential role of catechins in modulating neuroinflammatory processes through enhancement of anti-inflammatory pathways, particularly via IL-10 signaling. From a mechanistic perspective, the antioxidant and anti-inflammatory properties of catechins, supported by their chemical structure, may contribute to the maintenance of neuroimmune balance and neuronal function. However, these findings should be interpreted with caution. The study was conducted using a single dosage and a relatively short intervention period, and did not include detailed dose–response analysis, long-term safety evaluation, or comprehensive molecular pathway validation. Therefore, further studies with larger sample sizes, extended intervention durations, and more comprehensive biomarker and pharmacological analyses are required to confirm the long-term efficacy and safety of gambir-derived catechins and to better define their potential role in cognitive health strategies.

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