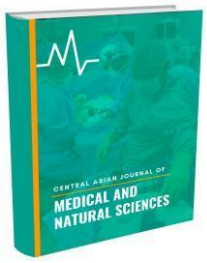

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Article

Reducing of Ethanol-Induced Liver Injury by *Camellia sinensis* Extract in Rats through Immunological and Oxidative Stress Pathways

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Abstract: *Camellia sinensis* exhibits potential hepatoprotective properties attributed to its high polyphenolic content, especially catechins. This study sought to assess the efficacy of C. sinensis extract in mitigating ethanol-induced hepatic injury in a rat model, with particular emphasis on biomarkers associated with oxidative stress and inflammatory responses. Adult male of Wistar rats were allocated into four experimental groups , control, ethanol-treated (ETOH), ethanol plus low-dose *C. sinensis* (ETOH + CSL) and ethanol plus high-dose *C. sinensis* (ETOH + CSH). Hepatic damage induced by ethanol was evaluated by quantifying serum concentrations of tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and malondialdehyde (MDA) as a key of oxidative stress biomarker. Ethanol exposure markedly increased TNF-α, IL-6, and MDA levels relative to the control group, indicating pronounced hepatic inflammation and oxidative stress. However, supplementation with *C. sinensis* extract dose-dependently reduced TNF-α and IL-6. Particularly, the high-dose *C. sinensis* group (ETOH + CSH) exhibited a significant reduction in both pro-inflammatory cytokines and MDA levels, emphasizing its strong role as anti-inflammatory and antioxidant. The conclusion show that *C. sinensis* extract, particularly at higher doses, can mitigate ethanol-induced hepatic damage by modulating inflammation and oxidative stress and these results support the potential therapeutic use of *C. sinensis* in treating alcoholic liver diseases.

Keywords: Camellia Sinensis, Inflammation, TNF-A, IL-6, Malondialdehyde

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1. Introduction

Camellia sinensis, the ancestor of green, black, and other teas, has been famous for its rich content of polyphenolic compounds, mainly catechins like *epigallocatechin gallate* (EGCG) [1]. These bioactive compounds are well known for their strong antioxidant, anti-inflammatory, and hepatoprotective activities [2]. As liver injury frequently caused by toxins, oxidative stress, or metabolic disorders continues to be a remarkable health burden, the interest in identifying natural therapeutic agents with less side effects is speeding up [3].

Green tea produced from the unfermented young leaves of *Camellia sinensis* has been extensively studied for its broad spectrum of bioactive properties which including antioxidant, anti-inflammatory, antitumor, antidiabetic, and cardioprotective effects [4]. The potent antioxidant capacity is primarily attributed to its high catechin content, with epigallocatechin gallate (EGCG) being the most abundant and effective compound in neutralizing free radicals and protecting cells against oxidative damage [5].

Camellia sinensis has demonstrated significant hepatoprotective effects across multiple models of liver injury. The plant's bioactive constituents exhibit multi-modal protection through inhibition of lipid peroxidation, suppression of pro-inflammatory cytokine expression (particularly TNF-α and IL-6) and enhancement of endogenous antioxidant enzyme activity [6]. This mechanistic profile positions *C. sinensis* as a promising therapeutic intervention for ethanol-induced hepatotoxicity, which fundamentally involves oxidative stress, inflammatory responses and direct hepatocellular damage [7].

Investigating the hepatoprotective properties of *Camellia sinensis* extract in experimental models could provide valuable insights for potential applications in alcoholic liver disease management. The liver being central to detoxification, metabolic regulation, and immune function is highly susceptible to damage from oxidative stress, toxic substances, and inflammatory effect [8]. Hepatic disorders including hepatitis, fibrosis, and cirrhosis represent significant worldwide health issues and are commonly treated using effective therapeutic interventions [9].

Pharmacotherapy is frequently elicit adverse effects, prompting increased interest in natural bioactive compounds possessing hepatoprotective and immunomodulatory properties as alternative therapeutic options. During hepatic ethanol metabolism, reactive oxygen species (ROS) production increases which inducing lipid peroxidation and subsequently promoting inflammatory responses and fibrotic progression in the liver [10]. Malondialdehyde (MDA) well-known biomarker of lipid peroxidation which provides a reliable measure of oxidative stress mediated cellular damage [11]. Natural antioxidants derived from *Camellia sinensis* have emerged as promising therapeutic agents capable of neutralizing these toxic oxidative processes [12]. This study aims to evaluate the hepatoprotective effects of *Camellia sinensis* extract against ethanol-induced liver damage in rats. This study tests the dose-dependent effects of *Camellia sinensis* extract on critical immunological and oxidative stress biomarkers in an experimental model of ethanol-induced hepatotoxicity, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and malondialdehyde (MDA), which are associated with ethanol-induced hepatic inflammation and oxidative injury.

2. Materials and Methods

Fresh leaves of *Camellia sinensis* (green tea) were obtained from local markets in Baghdad, Iraq. The plant material was subsequently shade dried at 25°C for 72 hours to maintain bioactive-compound integrity, followed by mechanical-homogenization into a fine powder using a sterilized electric grinder. For aqueous extraction, 100 g of powdered leaves was boiled in 1 L of distilled water (1:10 w/v) at 70 °C for 30 minutes, a protocol optimized to maximize polyphenol yield while minimizing degradation of catechins [13]. The mixture was filtered through Whatman No. 1 filter paper, and the supernatant was concentrated using a rotary evaporator at 40 °C under reduced pressure (200 mbar). The concentrate was lyophilized to obtain a dry powder (yield: ~12% w/w), which was stored in amber vials at 4 °C to prevent oxidation.

Animal Groups

Adult male Wistar rats (weighing 200–250 g) were obtained from a licensed animal facility. Rats were housed under standard laboratory conditions (22 ± 2 °C, 12 h light/dark cycle) with free access to standard pellet diet and water [14]. The study was conducted in accordance with "ethical guidelines for the care and use of laboratory animals", and all procedures were approved by "the Institutional Animal Ethics Committee (IAEC).

After a one-week acclimatization period, the rats were randomly divided into four groups (n = 6 per group) when the Group I (Control) which received distilled water only, group II (Ethanol) which received 40% ethanol at a dose of 6 g/kg/day orally for 6 weeks, Group III (Ethanol + Low-Dose C. sinensis) which received ethanol (6 g/kg/day) and *C.*

sinensis extract at 200 mg/kg/day where as last group as Group IV (Ethanol + High-Dose C. sinensis) which received ethanol (6 g/kg/day) and *C. sinensis* extract at 400 mg/kg/day. All treatments were administered orally by gavage once daily for six consecutive weeks. The extract was given 30 minutes after ethanol administration.

At the end of the treatment period, rats were fasted overnight and euthanized under anesthesia. Blood samples were collected via cardiac puncture, and seram were separated by centrifugation (3000 rpm, 10 minutes) and stored at −20 °C for biochemical analysis [15].

Biochemical Analysis

Serum levels of TNF-α and IL-6 were measured using enzyme-linked immunosorbent assay (ELISA) (Roche, Switzerland) kits according to the manufacturer's instructions. Malondialdehyde (MDA) levels in liver homogenates were measured as a marker of lipid peroxidation using the thiobarbituric acid reactive substances (TBARS) assay [16].

Statistical analysis

Statistical analysis of result using GrpaphPad prism software (Version 9) and Microsoft Excel 2020. All table and Figure were done using theses software programs and the data were analysis using ANOVA test with p value ≤ 0.05 and "independent t-test" method [17].

3. Results and Discussion

The current study demonstrated that chronic ethanol administration significantly elevated serum TNF-α levels in rats, consistent with the established role of TNF-α as a key mediator of ethanol-induced hepatic inflammation. A one-way ANOVA revealed a statistically significant difference in serum TNF-α levels among the experimental groups ($F = 26.28$, $p < 0.05$). The ethanol-treated group (ETOH) showed a substantial increase in TNF-α levels (100.7 ± 34.23 pg/mL) compared to the control group (17.90 ± 7.31 pg/mL, $p < 0.05$), indicating marked inflammation induced by ethanol. The present study demonstrated that chronic ethanol administration significantly elevated serum TNF-α levels in rats, reflecting a strong pro-inflammatory response. This is consistent with the known pathophysiological effects of ethanol, which promotes oxidative stress and activates Kupffer cells in the liver, leading to the release of inflammatory cytokines such as TNF-α [18]. In our study, rats treated with ethanol alone showed a marked increase in TNF-α levels compared to controls, confirming the inflammatory burden induced by ethanol toxicity as in Table 1.

Table 1. Statistical analysis ANOVA for all marker, p value ≤ 0.05.

Type	TNF-α	IL -6	MDA
P value	< 0.05	< 0.05	< 0.05
F	26.28	21.46	27.56
R square	0.5092	0.4586	0.5210

Co-treatment with Camellia sinensis extract significantly reduced TNF-α levels in a dose-dependent manner. The low-dose group (ETOH + CSL) showed reduced levels (85.20 ± 47.56 pg/mL) compared to the ethanol group, though this reduction was not statistically significant ($p = 0.2442$ vs. ETOH). However, the high-dose group (ETOH + CSH) exhibited a significant decrease (54.15 ± 24.27 pg/mL) when compared to both the ethanol group ($p < 0.05$) and the control group ($p < 0.05$), suggesting a strong anti-inflammatory effect at higher concentrations. The R^2 value of 0.5092 indicates that

approximately 51% of the variance in TNF-α levels can be explained by the treatment groups as in Table 2 and Figure 1.

Table 2. Statistical analysis of TNF-α, p value ≤ 0.05.

Groups/ type	CON	ETOH	ETOH + CSL	ETOH + CSH
N	20	20	20	20
Mean ± SD	17.90 ± 7.31	100.7 ± 34.23	85.20 ± 47.56	54.15 ± 24.27
P value		< 0.05[a]	< 0.05[a] 0.2442[b]	< 0.05[a, b]
75% Percentile	23.00	123.0	122.0	78.00
Median	16.50	103.0	70.50	47.00
Minimum	10.00	27.00	19.00	29.00
Maximum	31.00	145.0	174.0	111.0

*a: p value compared to CON group

**b: p value compared to ETOH group

Co-treatment with Camellia sinensis (CS) extract effectively attenuated TNF-α levels in a dose-dependent manner. While the low-dose group (ETOH + CSL) showed a moderate, non-significant reduction, the high-dose group (ETOH + CSH) exhibited a significant decrease in TNF-α, indicating a potent anti-inflammatory effect. These findings align with prior reports demonstrating the immunomodulatory and hepatoprotective properties of Camellia sinensis, largely attributed to its rich content of catechins—particularly epigallocatechin-3-gallate (EGCG) [19].

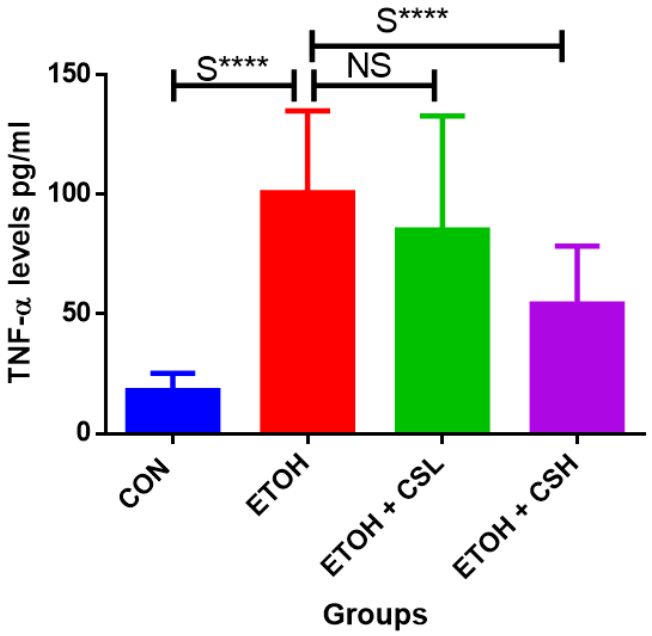

Figure 1. Results of TNF-α for all groups.

The mechanisms underlying this effect are multifaceted. EGCG has been shown to inhibit the activation of nuclear factor-kappa B (NF-κB), a key transcription factor

involved in the upregulation of pro-inflammatory cytokines including TNF-α and IL-6 [20]. By preventing NF-κB translocation to the nucleus, *Camellia sinensis* exerts complicated hepatoprotective effects through coordinated anti-inflammatory, antioxidant and immunomodulatory-mechanisms [21]. The extract significantly downregulates transcriptional activation of inflammatory mediators while suppressing key pro-inflammatory enzymes (COX-2 and iNOS) that are typically upregulated by ethanol-exposure [22]. Its potent antioxidant activity directly scavenges ethanol-derived reactive oxygen species (ROS), in this manner limiting oxidative damage and interrupting ROS-mediated activation of NF-κB and MAPK signaling pathways, a crucial mechanism for reducing TNF-α production [23]. Furthermore, C *sinensis* induces phenotypic modulation of hepatic macrophages, promoting a transition from pro-inflammatory M1 to anti-inflammatory M2 polarization [24]. This action simultaneously decreases inflammatory signaling while enhancing tissue repair processes, ultimately restoring hepatic immune homeostasis and providing protection against ethanol-induced liver injury [25].

The significant elevation of IL-6 levels in ethanol-treated rats observed in this study is consistent with its well-established role as a key pro-inflammatory cytokine involved in the pathogenesis of alcohol-induced liver injury [26]. Chronic ethanol exposure is known to activate hepatic immune cells, particularly Kupffer cells, which respond by releasing IL-6 along with other inflammatory mediators [27]. In our findings, rats in the ethanol group exhibited markedly higher IL-6 concentrations (182.20 ± 98.36 pg/mL) compared to controls (19.70 ± 9.96 pg/mL), highlighting the strong inflammatory response induced by ethanol toxicity as in Table 3 and Figure 2.

Table 3. Statistical analysis of IL-6, p value ≤ 0.05.

Groups/ type	CON	ETOH	ETOH + CSL	ETOH + CSH
N	20	20	20	20
Mean ± SD	19.70 ± 9.96	182.20 ± 98.36	119.60 ± 78.65	72.06 ± 43.62
P value		< 0.05[a]	< 0.05[a] 0.0330[b]	< 0.05[a, b]
75% Percentile	22.00	245.0	156.0	90.00
Median	16.50	174.0	104.5	73.50
Minimum	11.00	39.00	19.00	19.00
Maximum	42.00	370.0	277.0	189.0

*[a]: p value compared to CON group

**[b]: p value compared to ETOH group

Co-administration of Camellia sinensis extract significantly reduced IL-6 levels in a dose-dependent manner. The low-dose group (ETOH + CSL) showed a moderate but statistically significant reduction (119.60 ± 78.65 pg/mL), while the high-dose group (ETOH + CSH) exhibited a more pronounced decrease (72.06 ± 43.62 pg/mL), suggesting enhanced anti-inflammatory efficacy at higher concentrations. These results support the protective role of Camellia sinensis in modulating the inflammatory cascade triggered by ethanol exposure.

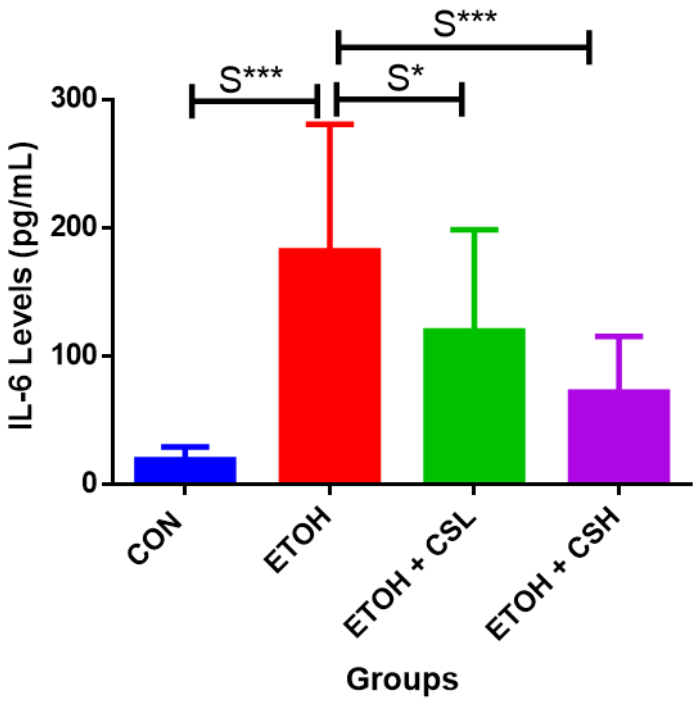

Figure 2. Results of IL-6 for all groups.

The suppression of IL-6 by Camellia sinensis can be attributed largely to the actions of its polyphenolic compounds, particularly epigallocatechin-3-gallate (EGCG) [28]. The hepatoprotective effects of *Camellia sinensis* are mediated through multiple interconnected pathways. Epigallocatechin gallate (EGCG) which the predominant catechin, utilizes potent anti-inflammatory activity by inhibiting critical signaling pathways including NF-κB and STAT3 which are central to IL-6 transcription and release [29]. Specifically EGCG blocks NF-κB activation and nuclear translocation thereby suppressing transcription of IL-6 and other pro-inflammatory genes [30]. Moreover, EGCG modulates innate-immune responses by inhibiting Toll like receptor 4 (TLR4) signaling which a primary pathway activated by ethanol that drives IL-6 production in hepatic tissues [31].

The extract's antioxidant ability complements these anti-inflammatory effects. Ethanol metabolism generates reactive oxygen species (ROS) that impair both oxidative stress and inflammatory signaling through redox-sensitive transcription factors [32]. Catechins particularly EGCG, directly scavenge these ROS, simultaneously reducing oxidative stress and indirectly decreasing IL-6 expression [33].

The results demonstrate these mechanisms through biochemical evidence. The ethanol-treated group (ETOH) showed markedly elevated malondialdehyde (MDA) levels (7.14 ± 3.52 μmol/L) which confirming significant lipid peroxidation resulting from chronic ethanol consumption. This oxidative damage occurs through ROS mediated oxidation of membrane poly-unsaturated fatty acids, with MDA serving dual roles as both a biomarker of oxidative stress and an active contributor to liver injury by maintaining inflammatory responses and cellular dysfunction.

Interestingly, the co-administration of Camellia sinensis extract reduced MDA levels in a dose-dependent manner. The low-dose group (ETOH + CSL) exhibited a partial reduction in MDA levels (5.32 ± 2.64 μmol/L) compared to the ethanol group, though this change was not statistically significant ($p = 0.0720$). This modest reduction suggests that lower doses of Camellia sinensis may exert some antioxidant effects but may not be sufficient to fully counteract the oxidative damage induced by ethanol. However, the high-dose group (ETOH + CSH) showed a significant decrease in MDA levels (1.96 ± 1.39

μmol/L), similar to the control group, reflecting a strong antioxidative effect at higher concentrations ($p < 0.05$ compared to the ethanol group) as in Table 4 and Figure 3.

Table 4. Statistical analysis of MDA, p value ≤ 0.05.

Groups/ type	CON	ETOH	ETOH + CSL	ETOH + CSH
N	20	20	20	20
Mean ± SD	1.14 ± 0.54	7.14 ± 3.52	5.32 ± 2.64	1.96 ± 1.39
P value		< 0.05[a]	< 0.05[a] 0.0720[b]	0.1068[a] < 0.05[b]
75% Percentile	1.900	9.500	7.200	2.200
Median	1.350	7.450	5.000	1.650
Minimum	0.5000	1.600	1.200	0.5000
Maximum	2.300	13.40	9.600	7.200

*[a]: p value compared to CON group

**[b]: p value compared to ETOH group

The protective effect of Camellia sinensis against oxidative damage can be attributed to its rich polyphenolic content, particularly epigallocatechin-3-gallate (EGCG). EGCG has potent antioxidant properties and has been shown to scavenge ROS, reducing oxidative stress and lipid peroxidation. By inhibiting lipoxygenase and cyclooxygenase, EGCG prevents the formation of reactive lipid radicals and reduces the downstream production of MDA [34]. Additionally, EGCG can upregulate antioxidant enzymes such as superoxide dismutase (SOD) and catalase, which further mitigate the oxidative burden [35].

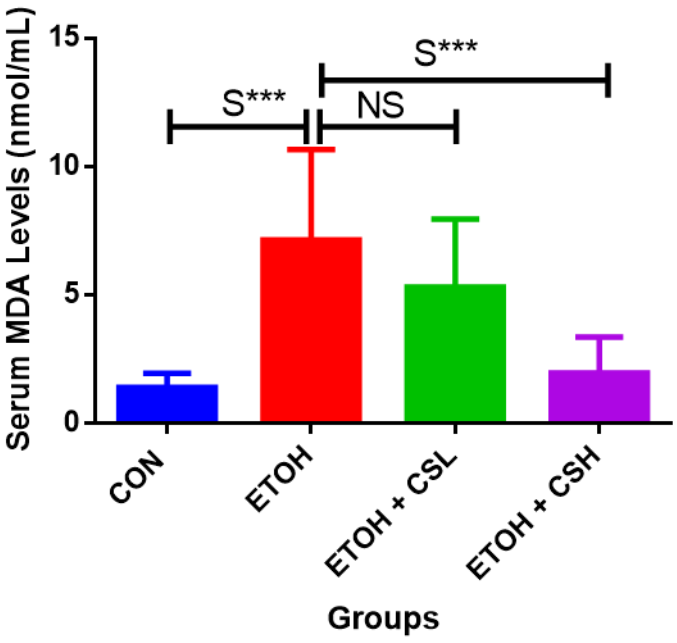

Figure 3. Results of MDA for all groups.

The dose responsive reduction in malondialdehyde (MDA) levels particularly the significant attenuation observed in the high dose *Camellia sinensis* group which demonstrates concentration dependent efficacy against ethanol induced oxidative damage. This protective-effect likely operates through dual mechanisms which including direct ROS scavenging by polyphenolic constituents and upregulation of endogenous antioxidant defense systems, including superoxide dismutase (SOD) and glutathione peroxidase (GPx) [36]. These results agree with previous studies that documenting the hepatoprotective capacity of *C. sinensis* across diverse experimental models of hepatic injury [37], [38].

4. Conclusion

The study demonstrates that *Camellia sinensis* extract show significant hepatoprotection in a rat model of ethanol induced hepatic injury. Treatment with C. *sinensis* particularly at higher doses, produced significant reductions in both pro-inflammatory mediators (TNF-α and IL-6) and oxidative stress biomarkers (MDA). These results indicate that the protective mechanism involves concurrent reduction of inflammatory pathways and oxidative damage. The dose dependent efficacy observed suggests that C. *sinensis* possesses substantial therapeutic potential as a natural intervention against alcohol related liver pathology

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