


Green Tea Polyphenols Extracted Using Natural Deep Eutectic Solvents (NaDES): Extraction Efficiency and Anti-Inflammatory Mechanisms - A Narrative Review

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Abstract: Inflammation involves complex immune signaling driven by cytokines, oxidative stress, and activation of pathways such as NF- κ B and MAPK. Green tea (*Camellia sinensis*) contains polyphenols, particularly catechins, that modulate these pathways, but extraction efficiency and stability depend strongly on solvent systems. NaDES have emerged as environmentally friendly alternatives to conventional solvents, offering improved solubility for polar phytochemicals. This narrative review summarizes current evidence on NaDES-based extraction of green tea polyphenols and their associated anti-inflammatory activities. Literature was identified through targeted searches of PubMed and Google Scholar using predefined keywords related to NaDES, green tea, catechins, extraction efficiency, and inflammatory pathways. Across studies, NaDES systems, especially choline chloride-glycerol and sorbitol-tartaric acid, yielded higher total phenolic and catechin levels than ethanol or water, often with ultrasonic-assisted extraction. NaDES-extracted green tea showed enhanced antioxidant activity and, in cell models, modulated inflammatory mediators including iNOS, COX-2, TNF- α , IL-1 β , and NF- κ B signaling. Evidence from non-NaDES studies provides complementary insight into downstream mechanisms such as Nrf2 activation and cytokine regulation. Overall, NaDES extraction offers a promising strategy to improve the recovery and biological performance of green tea polyphenols; however, available data remain preclinical, and further work is required to evaluate safety, pharmacokinetics, and formulation applicability.

Keywords: *Camellia sinensis*; NaDES; anti-inflammatory.

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1. Introduction

Inflammation is a fundamental protective response activated by pathogens, tissue injury, or chemical stressors. It involves coordinated immune cell recruitment and the release of cytokines and mediators that eliminate harmful stimuli and initiate tissue repair, presenting clinically as redness, swelling, pain, and functional impairment [1]. Key cytokines such as interleukin-1 β (IL-1 β), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α) activate intracellular signaling pathways including mitogen-activated protein kinases (MAPK), nuclear factor- κ B (NF- κ B), and Janus kinase (JAK), which collectively promote transcription of pro-inflammatory genes. When unresolved, inflammation may progress into chronic states linked to cardiovascular disorders, diabetes, neurodegeneration, and cancer [2-5].

Non-steroidal anti-inflammatory drugs (NSAIDs) remain widely used due to their ability to inhibit cyclooxygenase (COX-1 and COX-2), which are involved in prostaglandin synthesis [6,7]. Although selective COX-2 inhibitors reduce gastrointestinal toxicity, prolonged NSAID use still compromises mucosal protection and increases the risk of ulcers and bleeding [6], underscoring the need for safer long-term alternatives.

Natural bioactive compounds have therefore gained attention for their multi-target mechanisms and favorable safety profiles. Polyphenols, including quercetin, resveratrol, luteolin, and curcumin, exhibit antioxidant, immunomodulatory, and cytoprotective effects [8-11]. Green tea (*Camellia sinensis*) is particularly rich in catechins such as epigallocatechin gallate (EGCG), epigallocatechin (EGC), epicatechin (EC), and epicatechin gallate (ECG), which suppress iNOS and COX-2, downregulate TNF- α , IL-1 β , and IL-6, inhibit NF- κ B activation, and reduce oxidative stress by limiting reactive oxygen species (ROS) formation [12,13].

Optimal extraction of these catechins is critical to maximizing their biological potential. Conventional solvents such as ethanol, methanol, and acetone are effective but pose limitations due to volatility, flammability, and environmental concerns [14,15]. In response, NaDES have emerged as tunable, biodegradable extraction media composed of hydrogen bond donors (HBDs) and acceptors (HBAs), capable of dissolving a wide range of polar to semi-polar phytochemicals [16,17]. Evidence shows that NaDES often produces higher total phenolic content (TPC) and total flavonoid content (TFC) than traditional solvents, especially under ultrasound-assisted extraction [18-20].

The superior performance of NaDES is attributed to their supramolecular hydrogen-bond networks, which enhance solute-solvent interactions, and to the addition of controlled amounts of water (<50%) that decrease viscosity and improve mass transfer without disrupting the eutectic structure [21-25]. These physicochemical advantages align with the growing need for sustainable and efficient extraction platforms in natural product research.

Accordingly, this narrative review synthesizes evidence on NaDES-based extraction of *Camellia sinensis* polyphenols and examines corresponding anti-inflammatory mechanisms reported across *in vitro* and *in vivo* models. By integrating data from extraction chemistry and pharmacological studies, the review aims to provide an updated, critical perspective on how NaDES may enhance the recovery and biological activity of green tea catechins.

2. Methods

This work was conducted as a narrative review to summarize current evidence on NaDES for the extraction of green tea polyphenols and their anti-inflammatory mechanisms. A targeted literature search was performed exclusively through PubMed and Google Scholar covering the years 2015-2025. The search used predefined keywords and Boolean combinations, including: “herbs”, “green tea (*Camellia sinensis*)”, “anti-inflammatory”, and “NaDES extraction”. Articles were screened based on titles and abstracts to identify studies relevant to NaDES formulation, green tea extraction, catechin characterization, or mechanisms related to inflammation and oxidative stress. Full texts of eligible studies were then evaluated for methodological completeness and relevance. Studies were included if they provided primary experimental data on (i) NaDES preparation or extraction performance, or (ii) biological activities of green tea polyphenols in *in vitro* or *in vivo* models. Studies were excluded if they lacked primary data, did not involve NaDES or green tea, or presented insufficient methodological detail. Because this is a narrative review, no formal quality

assessment scale was applied; instead, the rigor of each study was evaluated qualitatively based on clarity of methods and appropriateness of analytical techniques. Extracted information was synthesized thematically to compare NaDES with conventional solvents and to integrate mechanistic findings across studies.

3. Results

A synthesis of the selected studies demonstrates that NaDES substantially enhances the extraction of secondary metabolites from *Camellia sinensis*, particularly catechin-rich polyphenols and flavonoids. Compared with conventional solvents such as ethanol, methanol, or water, NaDES consistently produced higher total phenolic content (TPC) and total flavonoid content (TFC), improved extract stability, and stronger antioxidant capacity. The magnitude of improvement varied across NaDES formulations, indicating that physicochemical characteristics such as viscosity, polarity, and hydrogen-bonding capacity strongly influence extraction performance.

Across multiple studies, a consolidated overview of NaDES composition, extraction parameters, and bioactivities observed in representative models has been established. Most investigations employed ultrasound-assisted extraction (UAE), which enhanced solvent penetration, promoted cavitation, and accelerated solute release. NaDES systems examined included betaine-urea, choline chloride-glycerol, sorbitol-tartaric acid, and glycerol-malic acid, each exhibiting distinct polarity balances and viscosities that contributed to differences in extraction efficiency. Formulations pairing choline chloride with polyols (e.g., glycerol, ethylene glycol) generally produced the highest TPC values, suggesting optimal matching between solvent polarity and catechin solubility.

Reported TPC values for NaDES-extracted green tea ranged from approximately 71.66 to 243 mg GAE/g dry weight, surpassing those obtained using ethanol or aqueous extraction by 10-40% depending on the system employed [18,19,26]. UAE combined with NaDES reduced the extraction time to 20-30 minutes, in contrast to conventional maceration requiring up to 24 hours, while maintaining high yields. Scanning electron microscopy (SEM) analyses supported these findings by revealing substantial structural disruption of plant cell walls after NaDES-based UAE, confirming enhanced mass transfer and intracellular compound release [26,27].

Chromatographic analyses using HPLC and UPLC-Q-TOF-MS consistently identified EGCG, EGC, ECG, and EC as the dominant catechins enriched in NaDES extracts [18,26,28]. These extracts exhibited superior antioxidant performance, as reflected in lower DPPH and ABTS radical-scavenging IC₅₀ values and higher FRAP activities compared with ethanol-based extracts, demonstrating stronger electron-donating and metal-reducing properties [28,29]. In several studies, the improved antioxidant activity correlated directly with increased catechin concentrations, reinforcing the relationship between extraction efficiency and functional potency.

Beyond *Camellia sinensis*, NaDES also enhanced the extraction of phenolics from other botanical matrices such as *Vaccinium myrtillus* (bilberry) leaves. Notably, NaDES-derived extracts incorporated into semi-solid formulations showed improved antioxidant stability and increased sun protection factor (SPF) [30] when combined with UV filters, demonstrating the multifunctional potential of NaDES for both extraction and formulation enhancement [29]. These findings underscore the broader applicability and versatility of NaDES across different plant systems and product types.

Table 1. Studies related to the use of NaDES in green tea extraction.

Study objective	Extraction method	Sample/model	NaDES system/comparator	Key compounds	Major findings	Mechanisms	Ref
TPC/TFC determination and antioxidant assays (DPPH, ABTS, FRAP)	UAE (50°C; 30 min; 1:20 w/v)	Green tea leaves; bilberry leaves	NaDES (betaine-urea, malic acid-glycerol, tartaric acid-sorbitol; ±30% H ₂ O) vs water and 50% ethanol	EGCG, EGC, ECG, phenolic acids	NaDES increased TPC/TFC and antioxidant capacity vs ethanol/water	Strong H-bonding improves solubility; enhanced ROS scavenging	[18]
SPF and antioxidant stability of NaDES formulations	UAE (50°C; 30 min)	Bilberry leaves; green tea leaves	NaDES (glycerol-malic acid; sorbitol-tartaric acid) ± UV filters	Catechins, polyphenols	Higher SPF stability, increased FRAP, lower DPPH IC ₅₀	NaDES protects antioxidants from UV-induced degradation	[29]
Flavonoid profiling (UPLC-QTOF-MS; HPLC)	Optimized UAE (268 s; 76°C; 43 mL/g)	Fagopyrum tataricum bran	NaDES (ChCl-ethylene glycol)	Rutin, quercetin, kaempferol	Highest flavonoid yield (40.29 mg/g)	H-bonding + cavitation increase mass transfer	[28]
TPC, catechin quantification, SEM microstructure	UAE (21 min; 461 W; ~40% H ₂ O)	Green tea leaves	NaDES (choline chloride-glycerol)	EC, EGC, ECG, EGCG	TPC ≈243 mg GAE/g; faster extraction vs ethanol	Ultrasound disrupts cell walls; water reduces viscosity for better diffusion	[26]
Optimization of flavonoid/tannin extraction (RSM)	UAE (20 min; 69°C; 900 W)	Spent tea leaves	Twelve NaDES tested; best = acetic acid-glycerol	Quercetin, catechin, EC	Improved TFC/TTC; 10-20% H ₂ O improved viscosity/mass transfer	H-bond network enhances solubility; viscosity reduction improves extraction	[27]

Table 2. Studies related to the use of NaDES in green tea for anti-inflammatory activity mechanism

Study Objective	Method/Model	Sample	Treatment	Key Compounds	Major Findings	Mechanisms	Ref
Anti-inflammatory activity in macrophages	RAW 264.7 + LPS	Murine macrophages	Green tea extract	Catechins, flavonoids	↓ NO, COX-2, iNOS, IL-1β, IL-6	NF-κB and MAPK inhibition	[13]
Anti-inflammatory activity in lung epithelial cells (ARDS model)	L2 cells + LPS	Mouse lung epithelial cells	Green tea extract (1.65-6.25 μg/mL)	Catechins	↓ NF-κB, NLRP3, TLR-4, RAGE; ↓ IL-12, TNF-α, CRP	TLR-4/RAGE → NF-κB suppression	[31]
Liver inflammation and intestinal barrier function	S100-induced AIH mouse model	C57BL/6J mice	Longjing tea extract (50-200 mg/kg)	EGCG, EGC, EC, ECG	↓ TNF-α, IL-17, IFN-γ; ↑ IL-10; improved tight junction proteins	LPS/TLR-4/MyD88/NF-κB inhibition; microbiota restoration	[32]
Skin inflammation (atopic dermatitis)	HaCaT + TNF-α/IFN-γ	Human keratinocytes	10-200 μg/mL extract	EGCG, EGC, EC, ECG, caffeine	↓ IL-2/IL-6; ↓ COX-2/iNOS; ↓ p65/STAT-1; MAPK inhibition	NF-κB and MAPK (JNK/ERK/p38) suppression	[33]
Effects on lipid metabolism and inflammation	Broiler chicken trial	Female broilers	Green tea extract 500 mg/kg	Catechins	↓ LPL; ↑ ATGL; no TNF-α/IL-6 increase	Improved lipid metabolism without inducing inflammation	[34]

Overall, as summarized in Tables 1 and 2, the compiled evidence confirms that NaDES extraction systems significantly improve the recovery, stability, and functional activity of green tea polyphenols. These enhancements are largely attributed to synergistic physicochemical mechanisms, including strong hydrogen-bond interactions between NaDES components and catechin hydroxyl groups, effective cell-wall disruption under ultrasound treatment, and

improved solvent penetration. Collectively, these results position NaDES as a promising, efficient, and environmentally sustainable extraction strategy for maximizing the bioactive potential of *Camellia sinensis*.

4. Discussion

4.1. Mechanistic basis of NaDES in enhancing bioactive extraction.

NaDES enhance the extraction of polar and semi-polar phytochemicals by forming supramolecular hydrogen-bond networks between hydrogen bond donors (HBDs) and acceptors (HBAs). These networks interact strongly with hydroxyl groups on phenolic compounds, thereby improving solubility and diffusion efficiency [18,26,27]. Comparative studies demonstrate that NaDES such as choline chloride-glycerol or choline chloride-ethylene glycol yield significantly higher total phenolic content (TPC) and total flavonoid content (TFC) than ethanol or water extraction [26] (Figure 1).

The addition of 20-40% water reduces viscosity and enhances mass transfer while maintaining NaDES integrity [26,27]. Ultrasonication further improves extraction by generating cavitation that disrupts plant cell walls, facilitating the release of catechins such as EGCG, EGC, EC, and ECG [26,28].

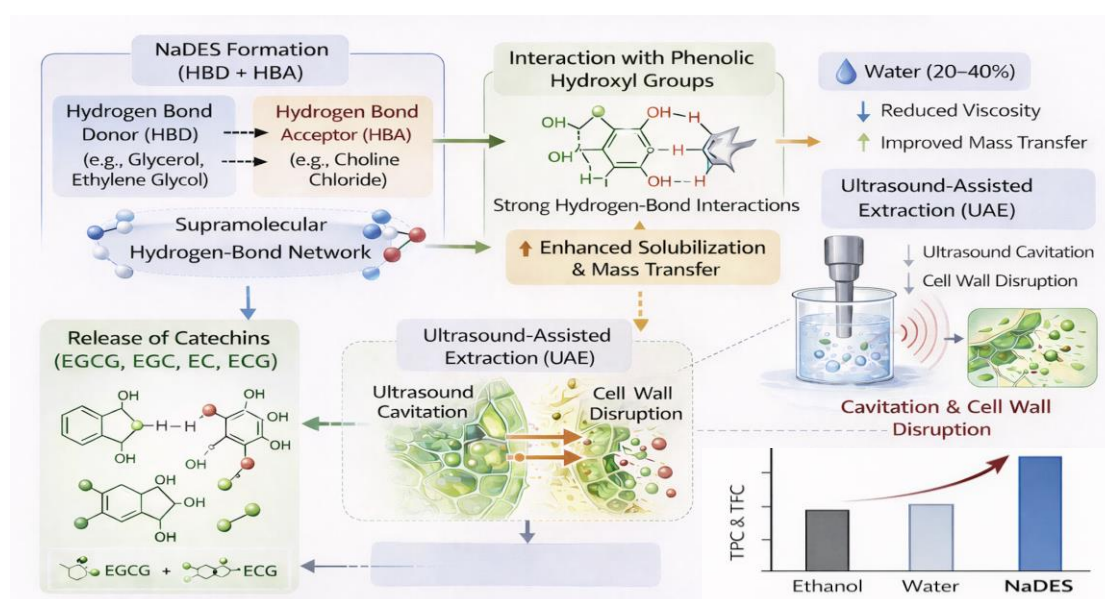


Figure 1. Mechanistic basis of NaDES in enhancing bioactive extraction (conceptual comparison).

4.2. Anti-inflammatory mechanisms of green tea polyphenols.

Catechins, particularly epigallocatechin gallate (EGCG), are the primary anti-inflammatory constituents of *Camellia sinensis* [35], acting on multiple molecular pathways relevant to acute and chronic inflammation. Evidence indicates that green tea polyphenols inhibit the activation of NF- κ B, MAPK (ERK, JNK, p38), and NLRP3 inflammasome signaling, thereby reducing the transcription of iNOS, COX-2, TNF- α , IL-1 β , and IL-6 [4,13,31,33].

NaDES-extracted green tea has been shown to suppress inflammatory markers in lung epithelial cells and keratinocytes, including inhibition of TLR-4, RAGE, and NF- κ B gene expression in LPS-induced models [31,33].

Beyond transcriptional regulation, green tea catechins also activate endogenous antioxidant defense pathways. EGCG upregulates Nrf2/HO-1, superoxide dismutase (SOD), and related cytoprotective enzymes, thereby reducing ROS accumulation and oxidative stress-mediated inflammation [36-38]. The combination of antioxidant and anti-inflammatory mechanisms underlies the broad pharmacological effects of green tea bioactives (Figure 2).

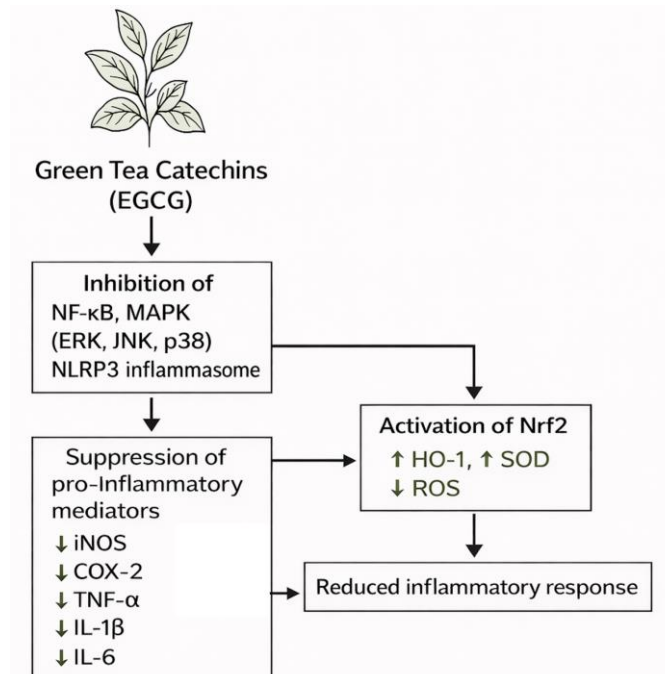


Figure 2. Anti-inflammatory mechanisms of green tea polyphenols (conceptual illustration).

4.3. Advantages and limitations of NaDES extraction.

NaDES extraction offers advantages including biodegradability, non-volatility, energy-efficient processing, and improved solubilization of phenolics [18,26-28]. However, several limitations remain significant barriers to wider application. One major challenge is the heterogeneity of NaDES formulations, as variations in viscosity, polarity, HBA/HBD ratios, and water content complicate cross-study comparisons and hinder standardization [26-28]. Another important limitation is the scarcity of toxicological and pharmacokinetic data. Only a few studies have investigated the safety profile and metabolic fate of residual NaDES components, raising concerns about their potential use in clinical or nutraceutical applications. In addition, *in vivo* validation remains limited. Although many studies have demonstrated promising *in vitro* results, evidence on the absorption, bioavailability, and long-term safety of NaDES-derived catechins remains insufficient. Scalability also poses a practical concern, as highly viscous NaDES systems may increase energy requirements and reduce efficiency at an industrial scale [39].

Further research should investigate toxicity, pharmacokinetics, solvent recovery, and cross-platform standardization to support the integration of NaDES into pharmaceutical development.

4.4. Therapeutic implications.

The converging evidence suggests that NaDES-based extraction enhances the pharmacological potential of green tea catechins by improving yield, stability, and antioxidant

capacity [18,26-28]. These extracts show promise for applications in nutraceuticals, dermatologicals, and phytotherapeutics targeting inflammation and oxidative stress-related disorders [10,40]. The incorporation of NaDES into extraction pipelines aligns with sustainable pharmaceutical practices and supports circular bioeconomy initiatives by reducing environmental impact. However, clinical translation requires further evidence, particularly regarding toxicological safety, bioavailability, formulation stability, and NaDES-solute interactions *in vivo* [41].

5. Conclusions

The evidence reviewed in this manuscript demonstrates that NaDES offer clear advantages for extracting polyphenols from *Camellia sinensis*, particularly through improved solubility, enhanced mass transfer, and increased catechin recovery under optimized ultrasonic-assisted conditions. These enhancements contribute to stronger antioxidant potential and may support improved anti-inflammatory activity. However, the available findings remain largely preclinical, with most studies limited to *in vitro* or *ex vivo* models and a few exploratory *in vivo* experiments.

Critical gaps persist, including limited toxicological evaluation of NaDES systems, insufficient data on pharmacokinetics and bioavailability of NaDES-derived catechins, and the absence of standardized protocols for solvent composition, water content, and extraction conditions. Variability among NaDES formulations also complicates cross-study comparisons and limits the generalizability of outcomes.

Given these limitations, claims regarding therapeutic or clinical utility should remain cautious. NaDES-based extraction represents a promising green technology with substantial potential for phytopharmaceutical development, but further research is needed to validate safety, optimize formulation stability, establish scalability, and determine whether enhanced extraction truly translates into superior biological activity *in vivo*. Continued interdisciplinary investigation will be essential to advance NaDES from a laboratory-scale innovation toward a standardized, evidence-based platform for producing high-quality green tea bioactives.

Author Contributions

Conceptualization, A.J.A. and H.R.; methodology, A.J.R.; data curation, H.R.; writing-original draft preparation, A.J.A.; writing-review and editing, H.R.; supervision, H.R. and M. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

Abbreviation	Definition
ABTS	2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) antioxidant assay
AD	Atopic Dermatitis
ATGL	Adipose Triglyceride Lipase
CAMP	Cathelicidin Antimicrobial Peptide
ChCl	Choline Chloride
COX	Cyclooxygenase
COX-2	Cyclooxygenase-2 (Inducible Isoform)
CRP	C-reactive Protein
DES	Deep Eutectic Solvent
DPPH	2,2-Diphenyl-1-picrylhydrazyl Radical Scavenging Assay
DW	Dry Weight
EC	Epicatechin
EG	Ethylene Glycol
EGC	Epigallocatechin
EGCG	Epigallocatechin Gallate
ELISA	Enzyme-Linked Immunosorbent Assay
FRAP	Ferric Reducing Antioxidant Power Assay
GAE	Gallic Acid Equivalent
HaCaT	Human Adult Keratinocyte Cell Line
HBA	Hydrogen Bond Acceptor
HBD	Hydrogen Bond Donor
HPLC-DAD	High-Performance Liquid Chromatography-Diode Array Detector
HO-1	Heme Oxygenase-1
iNOS	Inducible Nitric Oxide Synthase
IHC	Immunohistochemistry
IFN- γ	Interferon-gamma
IL	Interleukin
IL-1 β	Interleukin-1 beta
IL-6	Interleukin-6
IL-10	Interleukin-10
IL-17	Interleukin-17
JAK	Janus Kinase
LPL	Lipoprotein Lipase

Abbreviation	Definition
MAPK	Mitogen-activated Protein Kinase
MyD88	Myeloid Differentiation Primary Response 88
NaDES	Natural Deep Eutectic Solvent
NF- κ B	Nuclear Factor Kappa-B
NLRP3	NOD-Like Receptor Family Pyrin Domain Containing 3 (Inflammasome Component)
Nrf2	Nuclear Factor Erythroid 2-related Factor 2
NSAID	Non-steroidal Anti-inflammatory Drug
qRT-PCR	Quantitative Reverse Transcription Polymerase Chain Reaction
RAGE	Receptor for Advanced Glycation End-products
ROS	Reactive Oxygen Species
SEM	Scanning Electron Microscopy
SOD	Superoxide Dismutase
SPF	Sun Protection Factor
TFC	Total Flavonoid Content
TGF- β	Transforming Growth Factor-beta
TLR-4	Toll-like Receptor 4
TNF- α	Tumor Necrosis Factor-alpha
TPC	Total Phenolic Content
UPLC-Q-TOF-MS	Ultra-performance Liquid Chromatography-quadrupole Time-of-flight Mass Spectrometry
UAE	Ultrasound-assisted Extraction
UV	Ultraviolet
ZO-1	Zonula Occludens-1
REG3 β	Regenerating Islet-derived Protein 3-beta

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