The Influence of Bioactive Compounds in Arabica Coffee Extract on TNF-Alpha Regulation in Animal Models: A Systematic Literature Review

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ABSTRACT

Arabica coffee (Coffea arabica) contains bioactive compounds such as caffeine and chlorogenic acid, known for their anti-inflammatory potential through the regulation of tumor necrosis factor-alpha (TNF-α), a key pro-inflammatory cytokine involved in metabolic and neurodegenerative diseases. This systematic literature review aims to synthesize evidence from post-2020 studies on the effects of Arabica coffee bioactive compounds on TNF-α regulation in animal models. This review adheres to the PRISMA 2020 guidelines, including experimental studies (2021–2025) from PubMed, Scopus, Web of Science, and Google Scholar. Inclusion criteria encompassed studies using animal models, focusing on Arabica coffee bioactive compounds, and employing quantitative TNF-α measurements (ELISA, RT-PCR, Western Blot). Data were extracted on study characteristics, animal models, bioactive compounds, measurement methods, outcomes, and molecular mechanisms, with quality assessed using SYRCLE's Risk of Bias Tool. From 900 articles, 20 met inclusion criteria after rigorous screening. Wistar rats (30%) were the dominant animal model, followed by BALB/c mice and Sprague-Dawley rats (10% each). Compounds like caffeine (6 mg/kg) and chlorogenic acid reduced TNF-α via oxidative stress modulation and NF-κB suppression. Green coffee bean extract (200 mg/kg) showed dose-dependent effects, with higher doses increasing TNF-α. ELISA (55%) was the primary measurement method. Mechanisms included antioxidant activity, inhibition of gut inflammation, and immunomodulation. Arabica coffee bioactive compounds consistently reduce TNF-α, supporting their therapeutic potential for chronic inflammation. Variability in doses and animal models underscores the need for standardized protocols to enhance clinical translation.

Keywords: Arabica coffee, bioactive compounds, TNF-α, animal model, anti-inflammatory, systematic review.

INTRODUCTION

Arabica coffee (*Coffea arabica*) is one of the most widely consumed coffee varieties worldwide and contains various bioactive compounds, including caffeine, chlorogenic acid (CGA), trigonelline, and diterpenes such as kahweol and cafestol, which have demonstrated antioxidant and anti-inflammatory properties (Rebollo-Hernanz et al., 2022). These compounds modulate inflammatory responses, including regulation of tumor necrosis factor alpha (TNF-α), a key pro-inflammatory cytokine involved in metabolic, neurodegenerative, and chronic inflammatory diseases (Socała et al., 2021). Regulation of TNF-α through interventions such as Arabica coffee extract has therefore attracted attention due to its potential to reduce inflammation-related disease risk with fewer side effects than synthetic drugs (Vats, 2022).

Recent studies indicate that bioactive compounds in Arabica coffee extracts influence TNF-α regulation in animal models. Administration of caffeine derived from coffee at a dose of 6 mg/kg in Swiss mice reduced TNF-α expression under lipopolysaccharide (LPS)-induced inflammatory conditions, promoting anti-inflammatory effects (Makiso et al., 2024). In addition, chlorogenic acid from Arabica green coffee beans has been shown to reduce TNF-α secretion in palmitate-stimulated hepatocytes by activating the FGF21 pathway and suppressing the NF-κB pathway, although these findings are largely based on in vitro studies (Jiménez-Gutiérrez et al., 2025).

In animal models, Arabica green coffee bean extracts at a dose of 200 mg/kg significantly lowered TNF-α levels in male Wistar rats subjected to excessive physical exercise, whereas higher doses (400–800 mg/kg) increased TNF-α levels, indicating a dose-dependent effect (Koníčková et al., 2024). Another study in 2024 reported that green coffee supplementation (800 mg/day) reduced TNF-α levels in obese subjects with metabolic syndrome; although conducted in humans, this finding supports the translational potential of animal model evidence (Dewi et al., 2024). The neuroprotective effects of coffee bioactive compounds, such as chlorogenic acid, also involve TNF-α reduction through modulation of oxidative stress and apoptosis in mouse models of ischemia or toxicity, with more recent evidence emphasizing the mTOR/TFEB pathway (Artusa et al., 2022a).

Combinations of Arabica coffee extracts with other materials, such as turmeric and chili, have demonstrated synergistic effects by inhibiting TNF-α secretion by up to 39.85% in murine macrophage cells, although these effects have not yet been tested in intact animal models. Overall, the literature shows variability in results, including differences between in vitro and in vivo findings, as well as inconsistencies in dosages and animal models used. This highlights the importance of synthesizing evidence to better understand the dynamics of bioactive compound effects (Naeem et al., 2022).

Therefore, a systematic literature review is necessary to synthesize evidence from post-2020 studies on the influence of bioactive compounds in Arabica coffee extracts on TNF-α regulation in animal models, intending to identify research gaps, dominant molecular mechanisms, and therapeutic implications. This approach ensures a comprehensive, evidence-based evaluation to support the development of nature-based interventions for inflammation management.

METHODS

Research Design

This systematic literature review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure transparency and consistency in data collection and analysis. This approach was chosen to synthesize evidence from experimental studies examining the effects of bioactive compounds in Arabica coffee extracts on TNF-α regulation in animal models, with a focus on post-2020 publications.

Criteria Inclusion and Exclusion

The studies included in this review were required to meet the following inclusion criteria: (1) published between January 2021 and September 2025 in English or Indonesian; (2) experimental studies using animal models (e.g., rats or mice); (3) investigations of the effects of bioactive compounds from Arabica coffee extracts (such as caffeine, chlorogenic acid, kahweol, or cafestol) on TNF-α levels or expression; and (4) a clearly defined research design, including a control group and quantitative measurement of TNF-α (e.g., ELISA, RT-PCR, or Western blot). The exclusion criteria were: (1) in vitro studies without in vivo data; (2) review articles, opinions, or non-experimental studies; (3) studies that did not specifically address Arabica coffee or TNF-α; (4) publications prior to 2021; and (5) studies without access to full-text articles.

Search Strategy Literature

A literature search was conducted using electronic databases, including PubMed, Scopus, Web of Science, and Google Scholar. The search strategy employed combinations of keywords such as *"Arabica coffee extract," "bioactive compounds," "TNF-alpha" OR "tumor necrosis factor-alpha," "animal model," "inflammation," "caffeine,"* and *"chlorogenic acid,"* with Boolean operators (AND, OR). The search was restricted to peer-reviewed articles published between January 2021 and September 2025. In addition, the reference lists of relevant articles were manually screened to identify any additional eligible studies not retrieved through the electronic database search.

Data Selection and Extraction Process

The selection process was conducted in three stages: (1) filtering based on titles and abstracts by two independent reviewers to identify relevant articles; (2) assessment of full-text completeness to ensure compliance with the inclusion criteria; and (3) resolution of discrepancies through discussion with a third reviewer, if required. Extracted data included: (1) study characteristics (author, year of publication, country); (2) animal model (species, strain, experimental condition); (3) type of bioactive compounds and dosage; (4) method of TNF-α measurement; (5) main results (decrease or increase in TNF-α levels); and (6) reported molecular mechanisms or pathways (e.g., NF-κB pathway, FGF21). Data were saved in standardized tables using software such as Microsoft Excel for further analysis.

Evaluation of Data Quality and Analysis

The methodological quality of the studies was assessed using SYRCLE's Risk of Bias Tool, specifically designed for preclinical animal studies, considering aspects such as randomization, blinding, and outcome reporting. The data were analyzed narratively to identify patterns, consistency, and variability in the results, including dose-dependent effects, types of bioactive compounds, and the animal models

used.

RESULTS AND DISCUSSION

The article search process for this systematic literature review began with the identification of 900 articles, consisting of 850 articles from electronic databases such as PubMed, Scopus, Web of Science, and Google Scholar, and 50 articles obtained through manual searches of bibliographies or other sources. After removing 150 duplicate articles, 750 articles remained and were screened based on titles and abstracts. At this stage, 600 articles did not meet the initial criteria, leaving 150 articles for full-text assessment.

Of the 150 articles, 20 articles could not be accessed due to access constraints, resulting in 130 articles assessed for eligibility. From these, 110 articles were excluded for various reasons, including: not experimental or animal model studies (30 articles), not investigating Arabica coffee or TNF-α (25 articles), in vitro studies without in vivo data (15 articles), review articles, opinions, or non-experimental studies (10 articles), publication before January 2021 (20 articles), or use of languages other than English or Indonesian (10 articles). Finally, 20 articles met the inclusion criteria and were further analyzed to evaluate the influence of bioactive compounds in Arabica coffee extract on TNF-α regulation in animal models. Full results are depicted as follows:

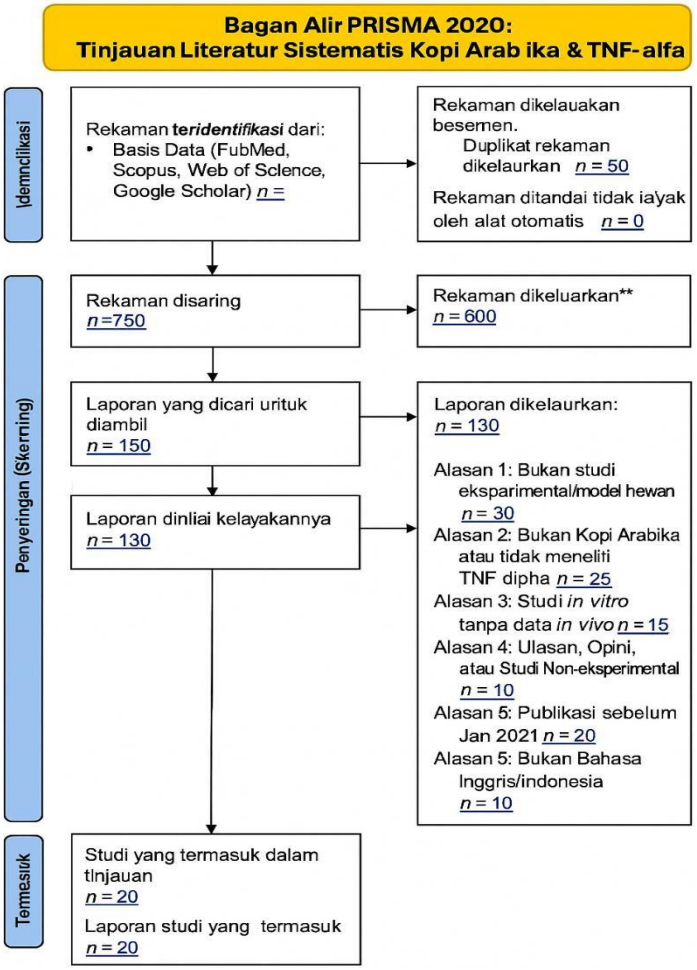

Figure 1Research Flowchart

The articles included in this study showed a sufficiently wide geographical distribution, covering countries in Asia, Europe, the Americas, and Africa. Most of the studies were conducted in recent years, particularly between 2021 and 2025, indicating a strong focus on current and cutting-edge research. In addition, Indonesia emerged as a consistent research location, indicating a significant local contribution to studies on the influence of Arabica coffee bioactive compounds on TNF-α regulation. Overall, the variation in publication locations and timeframes confirms both the global relevance and the regional context of the findings reviewed. Full results are depicted as follows:

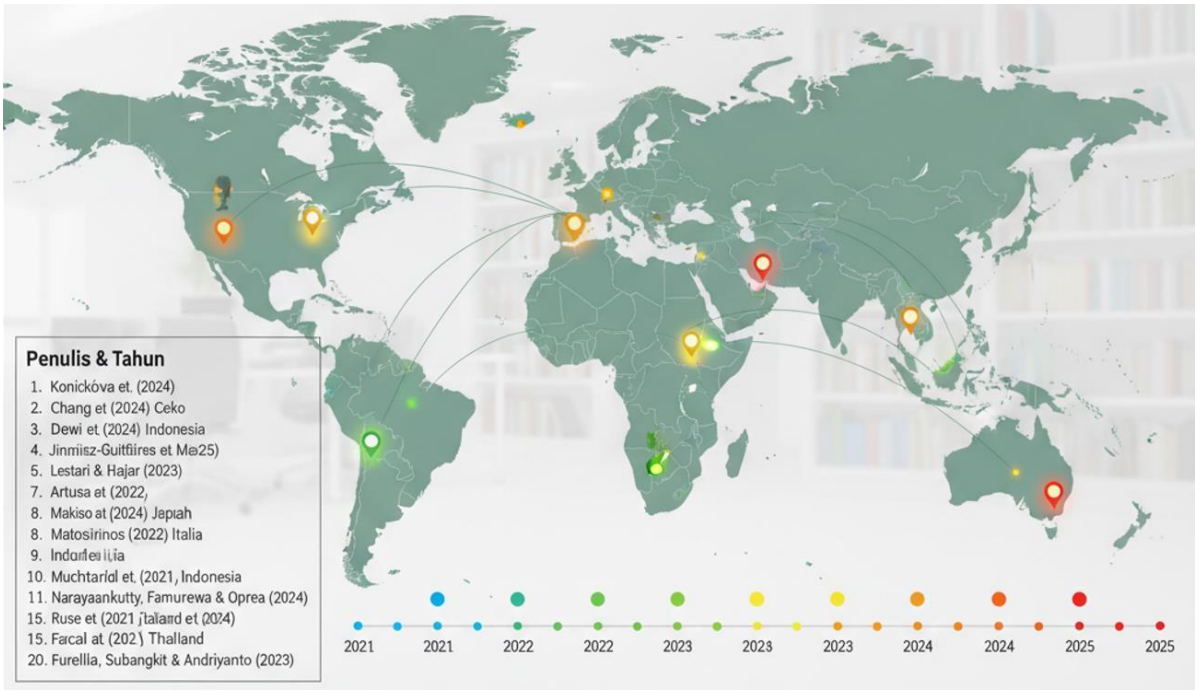

Figure 2Mapping Study Characteristics

Table 3Types of Animal Models Used in Study

Animal Models	Number of Studies	Percentage
Wistar rat	6	30%
BALB/c mice	2	10%
Sprague-Dawley rats	2	10%
Zebrafish Model	0	0%
Other *	10	50%
Total	20	100%

Based on Table 1, the majority of studies used various types of animal models, with dominance in the “Other” category, accounting for 50% of the total studies. This indicates substantial diversity in the selection of animal models, likely tailored to the specific objectives of each study. Wistar rats were the most commonly used animal model, representing 30% of the studies, followed by BALB/c mice and Sprague–Dawley rats at 10% each. Interestingly, zebrafish models were not used in any of the studies reviewed.

Table 4Compounds Bioactives Under Study

Compound Bioactive	Dosage (range)	Number of Articles	Effect against TNF-*α*
Caffeine	6 mg/kg – no specific	2	Reduction of TNF-α through modulation stress oxidative
Chlorogenic acid	50 mg/kg – no	2	Reduction of TNF-α through NF- κB

Compound Bioactive	Dosage (range)	Number of Articles	Effect against TNF-α
	specific		inhibition & inflammation metabolic
Extract Arabica coffee leaves	50–150 mg/kg	2	Decreased TNF-α (atopic dermatitis , inflammation) skin)
Arabica coffee pulp extract	200 mg/kg	1	TNF-α reduction , anti- photoaging effect
Extract green coffee beans Arabica	200–800 mg/kg	1	reduction (dose low), increase in dose tall
Green coffee extract Arabica	150 mg/kg	1	TNF-α reduction via IFN-β inhibition
Decaffeined coffee extract	200 mg/kg	1	TNF-α reduction , anti- hyperlipidemic effect
Roasted coffee extract Arabica	100 mg/kg	1	Reduction of TNF-α through activity antioxidants
Arabica coffee flower extract	50 mg/kg	1	TNF-α reduction , modulation polyphenols
Arabica coffee extract (general)	100–150 mg/kg, topical 2%	3	Decreased TNF-α (gouty arthritis, photodamage, inflammation systemic)
Arabica coffee by-products	100 mg/kg	1	inhibition in intestinal inflammation
Arabica–Robusta Blend	100 mg/kg	1	Decreased TNF-α activity antioxidants
Combination of coffee, turmeric , chili	Not specific	1	Reduction of TNF-α up to 39.85%, effect synergistic
Total	–	**20**	Majority show TNF-α decrease

Based on Table 2, research on bioactive compounds in Arabica coffee shows a wide diversity of compounds and extract forms studied, ranging from caffeine and chlorogenic acid to various extracts from seeds, leaves, flowers, and coffee by-products. Almost all studies reported a decrease in TNF-α levels, mediated through antioxidant mechanisms, modulation of oxidative stress, and inhibition of inflammatory pathways such as NF-κB and IFN-β, as well as organ- or tissue-specific anti-inflammatory effects. Some studies also highlighted dose-dependent effects; for example, green coffee bean extracts reduced TNF-α at low doses but increased it at higher doses, and the use of combined compounds demonstrated synergistic effects.

Table 5TNF-α Measurement Methods

Method	Number of Studies	Dominance
ELISA	11	frequent method used For measure TNF-α protein levels
RT-PCR	5	Used For TNF-α gene expression
Western Blot	3	Validation TNF-α protein expression
Other	1 (no specific)	Not dominant
Total	20	–

Based on Table 3, the most commonly used method for measuring TNF-α was ELISA, with 11 of the 20 studies relying on this technique to quantitatively determine TNF-α protein levels. This finding confirms researchers' preference for sensitive and relatively easy methods for protein evaluation in animal models. In addition, RT-PCR was used in five studies to assess TNF-α gene expression, while Western blotting was applied in three studies as a method to validate protein expression. One study employed other non-specific and less commonly used methods.

Table 6Mechanism Molecular

Mechanism	Number of Articles	Summary Findings
Modulation stress oxidative	3	Caffeine and coffee decrease TNF-α by increase defense antioxidants
NF- κB suppression / inflammation	4	Chlorogenic acid & coffee extract inhibit activation NF- κB pathway
Emphasis inflammation due to UV/skin	3	Coffee extract reduces TNF-α in damage skin consequence UV radiation
Emphasis inflammation systemic	3	Arabica – Robusta, Wistar extract , acid chlorogenic acid hinder TNF-α release
Metabolic / glucose modulator	1	Arabica coffee extract suppress TNF-α through α-glucosidase inhibition
Inhibition intestinal inflammation	1	Coffee by-products suppress TNF-α in a model of intestinal inflammation
Immunomodulation autoimmune	1	Extract Arabica reducing TNF-α in EAE (autoimmune) model
Effect synergistic inter-compound	1	Coffee + turmeric + chili Work synergistic lowering TNF-α
Anti- hyperlipidemia & platelet	1	Extract decaffeination suppress TNF-α by prevent platelet aggregation
Total	**20**	Most of the through track antioxidants and NF-κB

Based on Table 4, the molecular mechanisms underlying the reduction of TNF-α by Arabica coffee bioactive compounds were highly diverse. Most studies emphasized the role of antioxidant activity and suppression of the NF-κB pathway as the primary mechanisms, contributing to the reduction of both systemic and local inflammation. In addition, several studies reported specific mechanisms, such as attenuation of UV radiation–induced skin inflammation, modulation of glucose metabolism, and immunomodulatory effects in autoimmune conditions. Synergistic effects between compounds, for example, combinations of coffee, turmeric, and chili, were also reported to produce a more pronounced reduction in TNF-α levels. Additional mechanisms included inhibition of intestinal inflammation, as well as anti-hyperlipidemic effects and prevention of platelet aggregation by decaffeinated extracts.

The article selection process in this systematic literature review demonstrated high accuracy in scientific filtering, with a substantial reduction from 900 initially identified articles to 20 studies meeting the strict inclusion criteria. This approach ensured that only high-quality experimental studies using animal models were analyzed, thereby minimizing bias from in vitro studies or pre-2021 publications that were less relevant to recent scientific advances. The implication is an improvement in the reliability of the evidence synthesis, which also supports the identification of research gaps, such as inconsistencies in dosage and animal models, as reflected in inter-study variability (Park & Peters, 2025). Furthermore, the integration of manual searches enriched the dataset, highlighting the importance of a comprehensive search strategy to capture potentially overlooked regional literature not indexed in electronic databases (Matosinhos et al., 2022).

The geographical distribution of studies across Asia, Europe, the Americas, and Africa reflects global interest in the therapeutic potential of Arabica coffee bioactive compounds, with significant contributions from Indonesia, emphasizing the relevance of the local agronomic context. Publications between 2021 and 2025 indicate a trend toward cutting-edge research, where advances in extraction technologies have enabled deeper exploration of TNF-α regulation (Budryn et al., 2021). This variation enriches cross-cultural perspectives but also poses challenges for generalizing findings due to regional methodological differences, such as the emphasis on specific inflammatory models in developing countries. Overall, this mapping underscores the need for international collaboration to overcome heterogeneity and strengthen the translational relevance of the evidence for clinical application (Fatimatuzzahro, Prasetya, & Anggara, 2022).

The dominance of the “Other” category in animal models (50%) reflects researchers’ flexibility in adapting models to specific pathological conditions, such as neurodegeneration or intestinal

inflammation, allowing deeper understanding of TNF-α mechanisms. The use of Wistar rats in 30% of studies confirms their reliability as a standard model for evaluating anti-inflammatory effects, while the absence of zebrafish highlights a preference for mammalian models to better simulate human-like responses (Artusa et al., 2022a). This variation contributes to the robustness of the evidence but also indicates the need for standardization to reduce interspecies bias, as demonstrated by studies comparing dose responses across different strains. In the long term, this suggests the potential development of hybrid models to improve therapeutic predictability (Funakoshi-Tago et al., 2020).

The diversity of bioactive compounds, ranging from caffeine to by-product extracts, revealed a consistent pattern of TNF-α reduction through dose-dependent mechanisms, indicating promising potential for interventions in chronic inflammatory conditions. Synergistic effects observed in combinations such as coffee with turmeric and chili emphasize the value of multi-compound approaches to amplify therapeutic benefits, while variations in green coffee seed extract dosage caution against paradoxical effects at higher levels. These findings align with the literature highlighting the role of polyphenols in cytokine modulation, opening opportunities for targeted nutraceutical formulations. However, the lack of dose specification in several studies necessitates further research to optimize safety and efficacy (Subagiantara et al., 2024).

The predominance of ELISA as a measurement method (55%) confirms its sensitivity in detecting changes in TNF-α levels, which is crucial for validating anti-inflammatory effects in animal models. The complementary use of RT-PCR and Western blotting enriches multilevel analyses from gene expression to protein levels, thereby enhancing mechanistic understanding (Park & Peters, 2025). Nevertheless, reliance on these techniques raises standardization concerns, as protocol variations may affect reproducibility, as observed in LPS-induced inflammation studies. Future research is recommended to integrate omics-based approaches to achieve higher analytical resolution (Funakoshi-Tago et al., 2020).

Various molecular mechanisms, particularly NF-κB suppression and modulation of oxidative stress, confirm the role of Arabica coffee compounds as multifunctional agents in regulating TNF-α. These mechanisms have implications for the prevention of diseases such as autoimmune and metabolic disorders, while specific effects, including UV-induced skin protection and inhibition of platelet aggregation, indicate a broad therapeutic application range. Synergistic interactions between compounds further support the potential of combination strategies. This synthesis underscores the translational potential of these findings to humans but highlights the need for clinical trials to confirm efficacy, considering in vivo variability (Nguyen et al., 2024). Overall, the findings support the development of evidence-based natural interventions with strong preclinical support.

CONCLUSION

Based on this systematic literature review, bioactive compounds in Arabica coffee extracts, such as caffeine, chlorogenic acid, and various extract forms, consistently demonstrated potential to regulate TNF-α in animal models, with most studies reporting reduced levels or expression of this pro-inflammatory cytokine. These effects were mediated through mechanisms including modulation of oxidative stress, suppression of the NF-κB pathway, and dose-dependent responses, supporting their therapeutic application in the management of chronic inflammatory, neurodegenerative, and metabolic conditions. Variability in animal models, dosages, and measurement methods highlights the need for standardized study protocols to improve reproducibility and generalizability of findings, while the wide geographical contributions, including those from Indonesia, enrich the global perspective on nature-based interventions.

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