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Anti-inflammatory Potential of *Persea americana* (Avocado) Leaves: A Systematic Review of Mechanisms and Preclinical Evidence

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ABSTRACT

Chronic inflammation contributes to major degenerative diseases such as diabetes, cancer, and cardiovascular disorders, while conventional anti-inflammatory therapies often pose toxicity risks. Avocado leaves (*Persea americana* Mill.) are traditionally used to manage inflammatory conditions, yet their molecular mechanisms remain underexplored. This systematic review aimed to evaluate the anti-inflammatory activity of avocado leaves and synthesize current evidence on their underlying mechanisms. A systematic literature search was conducted in Google Scholar, PubMed, and ScienceDirect from May 2015 to May 2025 following PRISMA guidelines. Studies were screened based on predefined inclusion and exclusion criteria, and risk of bias was assessed using appropriate tools. From an initial 286 records, five preclinical studies met the eligibility criteria and were included in the final analysis. Avocado leaves contain flavonoids such as quercetin, catechin, and epicatechin and demonstrate anti-inflammatory effects through multiple pathways, including inhibition of NF-κB signalling and activation of Nrf2-mediated antioxidant responses. Preclinical models have demonstrated beneficial effects in carrageenan-induced edema, radioprotection, wound healing, and toxin-induced oxidative stress models, although clinical evidence remains absent. Overall, avocado leaves show promise as a multi-target anti-inflammatory candidate; however, well-designed clinical trials and standardized extract characterization are required to establish their therapeutic potential.

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ABSTRAK

Inflamasi kronis berkontribusi terhadap berbagai penyakit degeneratif seperti diabetes, kanker, dan gangguan kardiovaskular, sedangkan terapi antiinflamasi konvensional sering disertai risiko toksisitas. Daun alpukat (*Persea americana* Mill.) secara tradisional digunakan untuk menangani kondisi inflamasi, namun mekanisme molekulernya masih belum banyak dikarakterisasi. Tinjauan sistematis ini bertujuan mengevaluasi aktivitas antiinflamasi daun alpukat dan mensintesis bukti terkini mengenai mekanisme kerjanya. Pencarian literatur sistematis dilakukan pada basis data Google Scholar, PubMed, dan ScienceDirect untuk artikel yang terbit antara Mei 2015 hingga Mei 2025 dengan mengikuti pedoman PRISMA. Studi diseleksi berdasarkan kriteria inklusi dan eksklusi yang telah ditentukan, dan risiko bias dinilai menggunakan instrumen yang sesuai. Dari 286 rekaman awal, lima studi praklinis memenuhi kriteria dan dianalisis lebih lanjut. Daun alpukat mengandung flavonoid seperti quercetin, catechin, dan epicatechin serta menunjukkan efek antiinflamasi melalui berbagai jalur, termasuk inhibisi sinyal NF-κB dan aktivasi respons antioksidan yang dimediasi Nrf2. Model praklinis memperlihatkan efek menguntungkan pada edema yang diinduksi karagenan, radioproteksi, penyembuhan luka, dan stres oksidatif akibat toksikan, meskipun bukti klinis masih belum tersedia. Secara keseluruhan, daun alpukat menunjukkan potensi sebagai kandidat agen antiinflamasi multi-target; namun, uji klinis yang terancang baik dan karakterisasi ekstrak yang terstandar masih diperlukan untuk menegaskan potensi terapinya.

Kata Kunci: Daun alpukat; *Persea americana*; Anti-inflamasi; NF-κB; Nrf2; Preclinical studies

1. Introduction

Inflammation represents the body's natural defense response to pathogenic threats and tissue injury, characterized by classic symptoms including redness, heat, pain, and swelling. This process involves immune cells such as neutrophils, mast cells, and macrophages, along with inflammatory mediator release through cyclooxygenase (COX) and lipoxygenase (LOX) pathways [1],[2],[3]. While acute inflammation serves a protective function, chronic inflammation has emerged as a hallmark of various degenerative diseases with increasing prevalence in modern society [4],[5]. Chronic inflammatory conditions pose a significant global health burden. Recent epidemiological studies suggest substantial prevalence of inflammatory disorders worldwide, with chronic pain conditions affecting large populations across different regions [6]. These chronic inflammatory states contribute significantly to mortality through cardiovascular disease, diabetes, and cancer, representing a major public health challenge [7],[8].

At the molecular level, inflammation involves complex signaling pathways regulated by nuclear factor-kappa B (NF-κB), which controls pro-inflammatory gene expression including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), and inducible nitric oxide synthase (iNOS) [9]. Overactivation occurs due to oxidative stress from disrupted equilibrium between reactive oxygen species generation and antioxidant defense systems [10], [11]. Conventional NSAIDs and glucocorticoids, while effective, present significant limitations including gastrointestinal, cardiovascular, and long-term toxicity risks, driving the search for safer natural alternatives. [12],[13].

Several studies have demonstrated anti-inflammatory potential of medicinal plants. Research has shown anti-inflammatory activity of *Azadirachta indica* through NF-

κB and COX-2 inhibition [14], while other studies reported effects of *Curcuma longa* flavonoids in inflammation models [15]. However, these approaches showed limitations regarding molecular target selectivity and dose-related side effects. Recent phytopharmacological research has identified bioactive compounds such as flavonoids, polyphenols, and terpenoids exhibiting anti-inflammatory activity through multiple pathway modulations [16],[17].

Avocado (*Persea americana* Mill.) has been extensively cultivated worldwide, including in Indonesia [18]. While avocado fruit has been well-studied for its nutritional properties, exploration of avocado leaves remains limited despite their traditional use in treating inflammatory conditions such as rheumatism and joint pain [19]. Preliminary studies suggest that avocado leaves contain bioactive compounds with antioxidant and potential anti-inflammatory properties [20]. Limited research has demonstrated anti-inflammatory activity in rat paw edema models [21],[22]. However, significant knowledge gaps remain regarding comprehensive characterization of active compounds, molecular mechanisms of action, standardized extraction methods, and safety profiles for clinical applications.

This systematic review aims to evaluate the anti-inflammatory activity of avocado leaves (*Persea americana* Mill.) and their underlying molecular mechanisms to provide scientific foundation for their potential development as natural anti-inflammatory agents.

2. Methods

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive literature search was performed across three electronic databases: Google Scholar, PubMed, and ScienceDirect for articles published between May 2015 and May 2025. The search strategy combined Medical Subject Headings (MeSH) terms and free-text keywords using Boolean operators: ("Persea americana" OR "avocado leaves") AND ("anti-inflammatory" OR "inflammation" OR "inflammatory") AND ("phytochemical" OR "bioactive compounds" OR "flavonoids" OR "quercetin" OR "catechin"). The final search was conducted on May 1, 2025, and reference lists of included studies were manually searched for additional relevant publications.

Inclusion criteria comprised original research articles published in English investigating anti-inflammatory properties of *Persea americana* leaves, including in vitro, in vivo, or clinical studies published between May 2015 and May 2025 from peer-reviewed journals with full-text availability. Exclusion criteria included studies focusing solely on avocado fruit/oil without leaf investigation, review articles, conference abstracts, case reports, non-English publications, studies without clear anti-inflammatory endpoints, and duplicate publications.

Two independent reviewers conducted the screening process based on titles and abstracts, followed by full-text evaluation of potentially eligible studies. Disagreements were resolved through discussion or consultation with a third reviewer when necessary. Data extraction was performed independently using a standardized form including study characteristics, sample preparation methods, study populations, intervention details, outcome measures, and key findings. Risk of bias assessment was conducted using SYRCLE's Risk of Bias tool for animal studies and adapted quality assessment criteria for laboratory studies, evaluating selection, performance, detection, attrition, and reporting bias.

Due to heterogeneity of study designs and outcome measures, a qualitative narrative synthesis was performed, organizing results by study type and outcomes. The initial search yielded 286 records (PubMed: 24, ScienceDirect: 135, Google Scholar: 127). After removing 25 duplicates, 261 records were screened, with 246 excluded based on title/abstract review. Fifteen full-text articles were assessed for eligibility, and ten were excluded due to insufficient focus on anti-inflammatory activity (n=5), review nature (n=3), or methodological limitations (n=2). Five studies met the inclusion criteria and were included in the final analysis (**Figure 1**).

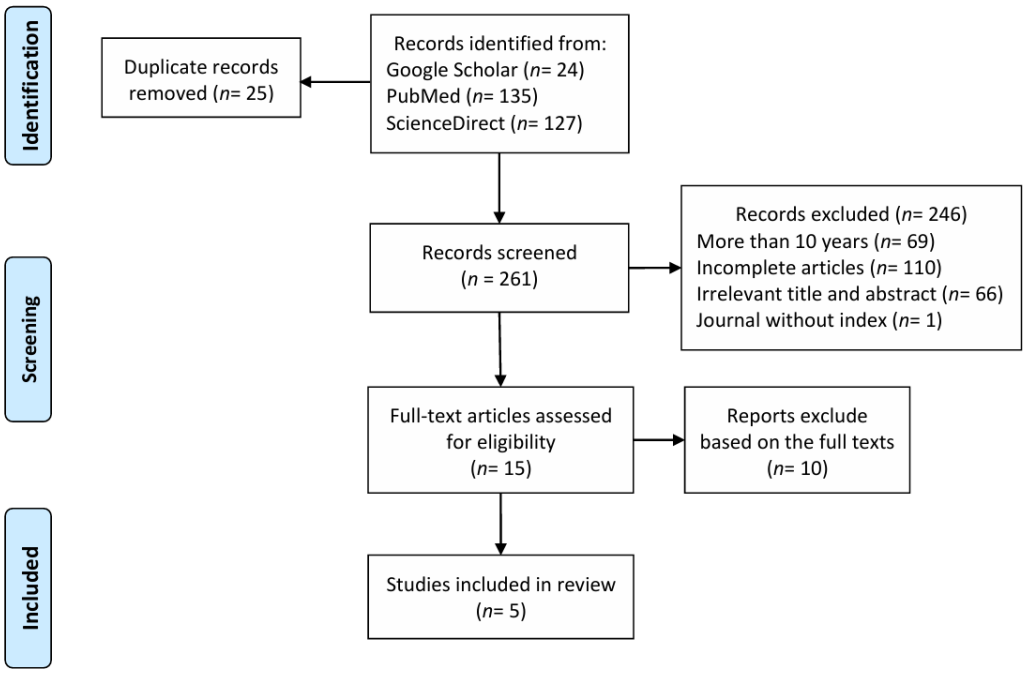

Figure 1. The flow chart of the identification and selection process.

3. Results and Discussion

Inflammation represents a complex biological immune response to various harmful stimuli, including microbial infections, tissue injury, or toxic substances. This evolutionarily conserved process serves the fundamental purpose of eliminating the causative agents of cellular damage and initiating tissue repair mechanisms. However, when inflammation becomes chronic or dysregulated, it can serve as the underlying pathophysiological foundation for numerous degenerative diseases, including diabetes mellitus, cancer, and cardiovascular disorders [23]. The inflammatory cascade is orchestrated by a sophisticated network of mediators, including pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β), which are predominantly produced by activated immune cells including macrophages, dendritic cells, and lymphocytes [24],[25],[26]. These cytokines function as key signaling molecules that coordinate the recruitment and activation of inflammatory cells, regulate vascular permeability, and modulate the expression of acute-phase proteins, thereby amplifying the inflammatory response through positive feedback mechanisms [9].

One of the most critical regulatory pathways in inflammatory mechanisms involves the activation of Nuclear Factor-kappa B (NF-κB), a ubiquitous transcription factor that serves as a master regulator of inflammatory gene expression. Under

physiological conditions, NF-κB remains sequestered in the cytoplasm through its association with inhibitory proteins of the IκB family. Upon stimulation by inflammatory triggers such as lipopolysaccharide (LPS), pro-inflammatory cytokines, or oxidative stress, the IκB kinase (IKK) complex becomes activated, leading to phosphorylation and subsequent proteasomal degradation of IκB proteins. This liberation allows NF-κB dimers to translocate to the nucleus, where they bind to specific DNA sequences and induce the transcription of numerous inflammatory genes, including cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), which catalyze the production of prostaglandins and nitric oxide, respectively [27]. Beyond NF-κB signaling mechanisms, other critical pathways including the Janus kinase/signal transducer and activator of transcription (JAK/STAT) system and mitogen-activated protein kinase (MAPK) signaling cascades serve essential functions in inflammatory processes by controlling various cellular activities such as cell growth, maturation, programmed cell death, and the release of inflammatory molecules [28].

The relationship between inflammation and oxidative stress represents a fundamental pathophysiological mechanism that underlies numerous chronic diseases. Oxidative stress arises when cellular production of reactive oxygen and nitrogen species surpasses the scavenging ability of intrinsic antioxidant mechanisms, encompassing enzymatic defenders like superoxide dismutase, catalase, and glutathione peroxidase. The overproduction of ROS can directly trigger inflammatory responses through the activation of redox-sensitive transcription factors, particularly NF-κB, and by stimulating the secretion of pro-inflammatory cytokines from various cell types. Conversely, the inflammatory process itself generates additional ROS through the activation of NADPH oxidase in phagocytes and the induction of iNOS, creating a self-perpetuating pathological cycle that exacerbates both oxidative damage and inflammatory responses [29],[30]. This bidirectional relationship between oxidative stress and inflammation has profound implications for therapeutic interventions, as compounds that can simultaneously target both pathways offer superior therapeutic potential compared to those with singular mechanisms of action [31].

Characteristics of Included Studies

The main characteristics of the five preclinical studies on avocado leaves included in this systematic review are summarized in **Table 1**.

Table 1. Summary of included studies on the anti-inflammatory activity of *Persea americana* leaves

No	Study Title	Research Method	Bioactive Compounds	Anti-inflammatory Mechanism	Reference
1	Nutritional, phytochemical and functional properties of avocado (*Persea Americana* Mill) leaf: Evaluation of its derivative extraction	Comparative analysis of extraction techniques (flour, aqueous extract, protein isolate, hydrolysates)	Phenols, flavonoids, saponins, tannins, terpenoids, proteins, minerals	Antioxidant activity through free radical scavenging and oxidative stress reduction in inflammation pathways	[20]

2	Anticlastogenic, radiation antagonistic, and anti-inflammatory activities of *Persea americana* in albino Wistar rat model	*In vivo* (Wistar rats), oral hydroalcoholic extract post X-ray exposure	Quercetin, apigenin, isorhamnetin, rutin, saponins, terpenoids	COX-2 inhibition and reduced ROS production during radiation exposure	[32]
3	Gas chromatography-mass spectrometry profiling and analgesic, anti-inflammatory, antipyretic, and antihyperglycemic potentials of *Persea americana*	*In vivo* (Carrageenan-induced paw edema)	Quercetin, isorhamnetin, luteolin, fatty acids, phenolics, tannins	Inhibition of carrageenan-induced edema through prostaglandin modulation	[21]
4	*Persea americana* leaf extract promotes wound healing by inhibiting NF-κB 1	*In vivo* + *in silico* (Wistar rats, network pharmacology, molecular docking)	Quercetin, catechin, epicatechin, alkaloids, flavonoids, phenols, saponins	NF-κB1 inhibition with cytokine and MMP down-regulation for wound healing	[33]
5	Ameliorative potentials of *Persea americana* leaf extract on toxicants - induced oxidative assault in multiple organs of wistar albino rat	*In vivo* (Wistar rats), toxin-induced (CCl4, rifampicin	Polyphenols, flavonoids	Nrf2 pathway activation enhancing antioxidant enzymes (SOD, catalase, GSH) and normalizing serum biomarkers	[34]

Phytochemical Composition of *Persea americana* Leaves

Studies indicate that the phytochemical composition of *Persea americana* leaves differs markedly from the fruit pulp, potentially contributing to distinct therapeutic properties for inflammatory conditions. Research has shown that unlike the fruit pulp, which contains predominantly monounsaturated fatty acids and phytosterols, the leaves exhibit a flavonoid-rich profile dominated by quercetin, catechin, epicatechin, and

phenolic acids [33], [35]. Adesola et al. [20] reported that flavonoid concentrations in leaf extracts were significantly higher compared to previously published fruit pulp values, with this compositional difference correlating with enhanced antioxidant activity in DPPH assays. Phytochemical analysis has identified unique compounds in leaf extracts, including C7 sugars and terpenoid derivatives not found in other plant parts, which authors suggest may contribute to therapeutic efficacy through membrane stabilization mechanism [33]. Research indicates that combined flavonoid compounds in leaf extracts demonstrate greater bioactivity than isolated compounds in inflammatory assays, supporting potential advantages of whole-plant extracts over single-molecule approaches, though the exact mechanisms of these interactions require further investigation [36],[37].

Proposed Anti-inflammatory Mechanisms

Studies suggest that avocado leaf extracts may modulate inflammatory signaling through multiple pathways. Rosa et al. [33] demonstrated NF-κB pathway inhibition in their wound healing model, reporting prevention of IκB-α phosphorylation and reduced nuclear translocation of p65 subunits, which correlated with decreased production of pro-inflammatory cytokines including TNF-α, IL-1β, and IL-6. The authors noted similarities to anti-inflammatory pathways observed in avocado fruit studies, though they reported higher flavonoid content in leaf extracts. Research indicates that quercetin in leaf extracts may interact with COX enzymes, though direct comparative selectivity data between COX-1 and COX-2 remains limited [33]. Ogunmoyole et al. [34] reported activation of Nrf2 signaling pathways by leaf extracts, which enhanced endogenous antioxidant defense systems including superoxide dismutase, catalase, and glutathione peroxidase in their toxicity model. The authors suggested this may help mitigate oxidative stress that contributes to inflammatory responses. These studies indicate potential for multi-pathway modulation, though comprehensive mechanistic studies and direct comparisons with conventional anti-inflammatory drugs are needed to establish clinical relevance [38].

Preclinical Models and Potential Applications

Multiple preclinical studies have evaluated the anti-inflammatory effects of avocado leaf extracts across different experimental models. In carrageenan-induced paw edema studies, Kumar et al. [32] reported that aqueous leaf extract administration resulted in reduction of edema volume in their Wistar rat model. Studies on wound healing have shown that 5–15% leaf extract formulations promoted healing through inflammation suppression and proliferative phase transitions, with authors documenting TGF-β upregulation and enhanced collagen maturation [33],[39]. Kumar et al. [32] also investigated radioprotective properties, reporting that pretreatment with leaf extracts significantly reduced radiation-induced dermatitis through reactive oxygen species scavenging and IL-10 preservation, an effect the authors noted had not been documented in other avocado plant parts. These studies suggest potential therapeutic applications across acute, chronic, and tissue-repair inflammation models, though the authors acknowledge that further research is needed to establish clinical relevance [40].

Despite promising preclinical results, several critical research gaps must be addressed to facilitate clinical translation of avocado leaf extracts. Studies have noted phytochemical variability across geographical sources, influenced by soil composition, seasonal variations, and post-harvest processing conditions, which researchers suggest necessitates development of standardized authentication protocols similar to those

established for avocado oil quality control. While acute toxicity studies indicate favorable safety profiles (LD50 >2000 mg/kg), comprehensive chronic toxicity assessments and potential herb-drug interactions, particularly with anticoagulants due to coumarin content, remain inadequately characterized [41]. Future research priorities should include Phase I/II clinical trials for topical formulations in osteoarthritis and wound care applications, isobolographic analysis for quantifying quercetin-catechin-terpenoid synergistic interactions, and development of nano-encapsulation strategies to enhance bioavailability of labile flavonoids. Additionally, translation of avocado leaf extracts into consumer-friendly delivery systems such as functional foods warrants investigation. Recent studies have successfully demonstrated the feasibility of incorporating plant leaf extracts into gummy formulations that maintain antioxidant activity while meeting pharmaceutical quality standards and sensory acceptability, suggesting similar approaches could enhance accessibility and compliance for avocado leaf-based products [42]. Researchers have highlighted the ecological valorization of avocado leaves as sustainable by-products of commercial cultivation, presenting opportunities for cost-effective therapeutic development while addressing agricultural waste management concerns. Studies suggest that integration of leaf extracts into functional foods or nutraceutical formulations could provide accessible adjunctive therapies for inflammatory conditions, expanding avocado's therapeutic applications beyond its established fruit-based health benefits [43].

4. Conclusion

This systematic review evaluated the anti-inflammatory potential of *Persea americana* leaves based on available preclinical evidence. The reviewed studies indicate that avocado leaves contain flavonoid-rich bioactive compounds that may modulate inflammatory pathways including NF-κB inhibition and Nrf2 pathway activation, with demonstrated effects in experimental models of carrageenan-induced edema, wound healing, and radioprotection. However, significant limitations exist including methodological heterogeneity across studies, lack of clinical trials, and inadequate characterization of standardization protocols and toxicity profiles. Future research should prioritize controlled clinical trials to establish human safety and efficacy, develop standardized extraction protocols, and conduct comprehensive toxicity assessments including potential drug interactions. These research directions are essential to advance the translational potential of avocado leaves as a sustainable source of natural anti-inflammatory agents.

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Conflicts of Interest:

The author declares that there are no conflicts of interest in this research.

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