



Therapeutic potential and structure–activity relationship of vanillin derivatives: advancements in anti-inflammatory drug development

Surendra Singh Gautam^{1*}, Dr. Prem Shankar Gupta²

^{1*}Research Scholar, Department of Pharmaceutical Chemistry, Teerthanker Mahaveer College of Pharmacy, Teerthanker Mahaveer University, Moradabad (U.P) India-244001 (ORCID: 0009-0006-3839-6444), Email Id: ssgautambuddha@gmail.com

²Associate Professor, Department of Pharmaceutics, Teerthanker Mahaveer College of Pharmacy, Teerthanker Mahaveer University, Moradabad, Uttar Pradesh, India-244001 (ORCID: 0000-0003-0951-9514)

Abstract

Chronic inflammation is a convergent driver of arthritis, inflammatory bowel disease, neuroinflammatory degeneration, metabolic liver injury, acute lung injury, and inflammation-associated cancer. Nonsteroidal anti-inflammatory drugs and selective cyclooxygenase-2 (COX-2) inhibitors remain the clinical mainstay, yet gastrointestinal, cardiovascular, and renal liabilities continue to motivate scaffold-level redesign. Vanillin (4-hydroxy-3-methoxybenzaldehyde), the principal phenolic aldehyde of *Vanilla planifolia* and a terminal cleavage product of curcumin, is a privileged, low-toxicity starting point for that redesign. Its three contiguous functional groups—the C4 phenolic hydroxyl, the C3 methoxy ether, and the C1 aldehyde—define a compact pharmacophore that can be oxidized, reduced, condensed, hybridized, or coordinated to metal centers without abandoning the guaiacol recognition motif.

This review synthesizes the chemistry, structure–activity relationship (SAR), molecular pharmacology, and translational constraints of vanillin and its anti-inflammatory derivatives. Parent vanillin suppresses nuclear factor kappa B (NF- κ B) by limiting I κ B kinase activation, I κ B- α phosphorylation, and p65 nuclear translocation; it concurrently dampens mitogen-activated protein kinase (MAPK) phosphorylation, inducible nitric oxide synthase (iNOS), COX-2, and the cytokines interleukin (IL)-1 β , IL-6, and tumor necrosis factor alpha (TNF- α), while supporting anti-inflammatory IL-4 in selected models (Wu et al., 2009; Kim et al., 2019; Kafali et al., 2024). The principal metabolites vanillic acid and vanillyl alcohol retain, and in several assays intensify, this profile, linking aldehyde oxidation or reduction to redox control and phospholipase A2 engagement (Bezerra-Filho et al., 2019; Kim et al., 2011; Wang et al., 2025). Medicinal-chemistry elaboration at the aldehyde—Schiff bases, hydrazones, chalcones, acetamide hybrids, 1,2,3-triazoles, pyrazolines, and thiadiazoles—and at the phenol—esters, ethers, and metal complexes—produces analogues with improved enzyme selectivity, membrane partitioning, and multi-target behavior. Electron-withdrawing aryl substituents, preservation of a hydrogen-bond donor near the guaiacol oxygen, and a moderately lipophilic linker emerge as recurrent SAR hotspots (Suleiman et al., 2025). In vivo, vanillin and close analogues reduce carrageenan edema, capsaicin- and allyl-isothiocyanate-evoked pain, trinitrobenzene sulfonic acid colitis, lipopolysaccharide lung injury, and microglial activation, often with a delayed rather than immediate peak, consistent with transcriptional rather than purely cyclooxygenase-level action (Boiko et al., 2019; Wu et al., 2009). The development case is therefore not that vanillin itself will replace indomethacin, but that the scaffold is an efficient platform for safer, multi-pathway anti-inflammatory leads. Priorities for the next design cycle are COX-2 versus COX-1 and 5-lipoxygenase selectivity panels, NLRP3 and Nrf2/HO-1 confirmation, metabolite identification, and formulation strategies that correct the rapid conjugation and modest oral exposure of the parent phenol.

Keywords: vanillin; vanillic acid; Schiff base; chalcone; structure–activity relationship; NF- κ B; COX-2; NLRP3; anti-inflammatory drug design

Introduction

1.1 The unfinished problem of anti-inflammatory therapy

Inflammation is a protective host program. When resolution fails, the same mediators that clear pathogens damage joints, epithelium, endothelium, and neurons. Prostaglandin E2 from COX-2, leukotrienes from 5-lipoxygenase (5-LOX), nitric oxide from iNOS, and the cytokines TNF- α , IL-1 β , and IL-6 form a redundant network under the transcriptional control of NF- κ B, activator protein-1, and the MAPK cascade (ERK1/2, JNK, p38). Inflammasome assembly, particularly NLRP3, adds a second-signal layer that converts pro-IL-1 β and pro-IL-18 into their mature forms and can culminate in gasdermin-D-dependent pyroptosis. A drug that blocks only one node of this network is easily bypassed; a drug that blocks cyclooxygenase indiscriminately pays for efficacy with mucosal injury and, in the case of several COX-2-selective agents, with thrombotic risk.

Natural phenolic aldehydes occupy a useful middle ground. They are weak-to-moderate direct enzyme inhibitors, but they repeatedly suppress the transcriptional amplification loop that sustains chronic inflammation. Vanillin is the most abundant and chemically tractable member of this class. It is already accepted as a food flavor (FEMA 3107), is produced at industrial scale by chemical synthesis from guaiacol or by lignin depolymerization, and

presents three orthogonal handles for analogue design. Those practical advantages explain why the last decade has produced Schiff bases, chalcones, triazoles, metal complexes, and nanocarriers built on the same 4-hydroxy-3-methoxybenzaldehyde core (Kafali et al., 2024; Suleiman et al., 2025).

1.2 Why a dedicated SAR review is needed

Existing reviews have mapped the pleiotropic biology of vanillin—anti-infective, wound-healing, neuroprotective, and anticancer—alongside its anti-inflammatory actions (Kafali et al., 2024; Bezerra-Filho et al., 2019). A parallel medicinal-chemistry review has catalogued synthetic routes and SAR hotspots across disease areas from 2014 to 2025 (Suleiman et al., 2025). What is still missing for the drug-development reader is a single argument that (a) separates parent, metabolite, and designed analogue, (b) assigns each structural change to a plausible anti-inflammatory mechanism, and (c) states which modifications are worth carrying into selective optimization. The present review is organized to that end. Claims that depend on a specific experiment are tied to the primary report; broader mechanistic syntheses are tied to the critical reviews that assembled them. Numerical values are reproduced only where the source abstract or full text states them, and they should be rechecked against the original tables before journal submission.

1.3 Scope and literature boundary

The review covers vanillin, o-vanillin, ethyl vanillin, vanillic acid, vanillyl alcohol, and designed derivatives in which the guaiacol ring is retained. Anti-inflammatory endpoints include cytokine and mediator suppression, COX and LOX inhibition, NF- κ B and MAPK signaling, inflammasome and pyroptosis markers, carrageenan and granuloma models, chemically induced colitis, acute lung injury, mastitis, and microglial neuroinflammation. Anticancer and antimicrobial data are cited only when they illuminate the same SAR hotspot or the same NF- κ B node. Clinical evidence remains sparse and is treated as a gap rather than as support.

2. Chemical Identity, Biosynthesis, and Physicochemical Starting Point

2.1 Structure and nomenclature

Vanillin is 4-hydroxy-3-methoxybenzaldehyde (C₈H₈O₃; molecular weight 152.15 g/mol). The benzene ring carries a hydrogen-bond-donating phenol at C4, a hydrogen-bond-accepting methoxy at C3, and an electrophilic aldehyde at C1. This arrangement is the guaiacyl substitution pattern of lignin and of ferulic acid. o-Vanillin (2-hydroxy-3-methoxybenzaldehyde) moves the phenol ortho to the aldehyde and thereby enables chelation; ethyl vanillin replaces the methoxy with ethoxy and is a synthetic flavor rather than a vanilla-bean constituent. Oxidation of the aldehyde yields vanillic acid (4-hydroxy-3-methoxybenzoic acid); reduction yields vanillyl alcohol. Both are circulating and urinary metabolites and are pharmacologically active in their own right (Bezerra-Filho et al., 2019). The aldehyde is the principal synthetic opportunity. Condensation with primary amines gives Schiff bases (azomethines); condensation with hydrazides gives hydrazones; Claisen–Schmidt reaction with acetophenones gives chalcones; copper-catalyzed azide–alkyne cycloaddition gives 1,2,3-triazoles; and Mannich reaction installs an aminomethyl handle on the activated phenol. Each of these transformations either masks the aldehyde, extends conjugation, or adds a second pharmacophore, and each changes lipophilicity, hydrogen-bonding pattern, and metabolic soft spots (Suleiman et al., 2025).

Table 1. Identity and medicinal-chemistry relevance of vanillin and its immediate congeners

Compound	Systematic name	Key change vs vanillin	Design implication
Vanillin	4-Hydroxy-3-methoxybenzaldehyde	Parent scaffold	NF- κ B / MAPK lead; aldehyde is the main vector
o-Vanillin	2-Hydroxy-3-methoxybenzaldehyde	Phenol moved ortho to CHO	Chelating Schiff-base ligand; often more NF- κ B active
Ethyl vanillin	3-Ethoxy-4-hydroxybenzaldehyde	Methoxy to ethoxy	Higher lipophilicity; flavor analogue, limited SAR data
Vanillic acid	4-Hydroxy-3-methoxybenzoic acid	Aldehyde oxidized	Major metabolite; NF- κ B, COX-2, NLRP3 activity
Vanillyl alcohol	4-Hydroxy-3-methoxybenzyl alcohol	Aldehyde reduced	Retains TRP-linked analgesia and edema control
Isoeugenol	2-Methoxy-4-propenylphenol	Side chain unsaturated	Docked at PLA2; comparator phenol, not a metabolite

Note. Structural relationships follow Bezerra-Filho et al. (2019), Kafali et al. (2024), and Suleiman et al. (2025). Isoeugenol is included because it was docked with vanillin and its metabolites at phospholipase A2.

2.2 Natural occurrence and industrial supply

Natural vanillin accumulates as vanillin glucoside in cured *Vanilla planifolia* and *Vanilla tahitensis* beans. Cure releases the aglycone by β -glucosidase action. Biotechnological routes from ferulic acid, eugenol, or isoeugenol,

and chemical routes from guaiacol plus glyoxylic acid, supply the bulk of world demand. For medicinal chemistry this supply chain is an advantage: the starting material is inexpensive, specification-controlled, and free of the supply risk that limits many plant alkaloids. Green methods—immobilized enzymes, microwave condensation, and solvent-minimized Schiff-base formation—have been applied to vanillin diversification over the last decade and are compatible with later scale-up (Suleiman et al., 2025).

2.3 Physicochemical liabilities that derivatives are asked to fix

Parent vanillin is a small, polar phenol. The phenolic hydroxyl is a conjugation site (glucuronide and sulfate), the aldehyde is a substrate for aldehyde dehydrogenases and for nonspecific protein binding, and aqueous solubility is adequate but membrane persistence is limited. These properties explain a recurring *in vivo* pattern: efficacy appears at tens to low hundreds of milligrams per kilogram, and the anti-edema effect is often clearer on the second day than in the first hours after carrageenan (Boiko et al., 2019). Derivative design therefore has three pharmacokinetic jobs as well as a pharmacodynamic one—slow conjugation, mask or replace the aldehyde, and add a lipophilic but still rule-of-five-compliant tail.

3. Structure–Activity Relationship: Hotspots on the Vanillin Core

SAR across vanillin series is consistent on one point and divergent on others. The consistent point is that small changes move potency a lot: a para-nitro versus a para-methoxy on an aniline-derived Schiff base, or an ortho versus para phenol, can separate an active analogue from a weakly active one (Suleiman et al., 2025). The divergent point is target identity. The same substitution that helps COX-2 occupancy may hurt 5-LOX, and the substitution that helps metal chelation may increase cytotoxicity. The hotspots below are therefore stated as anti-inflammatory hypotheses, not as universal rules.

Table 2. SAR hotspots on the vanillin scaffold for anti-inflammatory design

Hotspot	Tolerated change / favored change	Change that often weakens activity	Mechanistic reading
C4 phenol	Free OH, or OH unmasked after hydrolysis	Permanent cap without a prodrug rationale	H-bond donor; radical scavenging; Nrf2-relevant redox
C3 alkoxy	Methoxy retained; ethoxy sometimes tolerated	Deletion of alkoxy (loss of guaiacol)	Acceptor contact; tunes electronics of the phenol
C1 aldehyde	Imine, hydrazone, enone, triazole, carboxylic acid	Unmodified aldehyde if metabolic stability is required	Vector for hybridization; acid and alcohol are active metabolites
Aryl tail	p-NO ₂ , p-CF ₃ , p-F, restrained halogen	Bulky ortho-dialkyl without a pocket fit	EWG groups recur in COX-2-leaning series
Linker	Conjugated C=N or enone of moderate length	Very long flexible alkyl chains	Conjugation supports planarity and target π -stacking
o-Vanillin switch	Ortho OH when chelation is desired	Ortho OH if a non-chelating oral drug is the goal	Enables Cu, Zn, Ni, V complexes with added potency
LogP window	Approx. 2–4 for cellular analogues	LogP > 5 without a formulation plan	Balances membrane entry against solubility and promiscuity

Note. Hotspots are synthesized from Suleiman et al. (2025), Kafali et al. (2024), Boiko et al. (2019), and Demirbağ et al. (2025). They are design heuristics, not quantitative Free–Wilson coefficients.

3.1 The phenolic hydroxyl is necessary but not sufficient

Antioxidant assays assign the hydrogen-atom transfer capacity of vanillin primarily to the C4 hydroxyl, assisted by the ortho methoxy that stabilizes the resulting phenoxyl radical. Because NF- κ B and NLRP3 are redox-sensitive, this chemical fact is pharmacologically relevant: scavenging is not the whole anti-inflammatory mechanism, but it lowers the reactive-oxygen input that keeps those pathways switched on (Bezerra-Filho et al., 2019; Kafali et al., 2024). Esterification of the phenol can improve absorption if the ester is cleaved in plasma or tissue; a non-hydrolyzable ether generally costs antioxidant activity and should be justified by a gain in enzyme affinity. Schiff-base series that keep a free phenol on the vanillin ring, and add a second polar group on the aniline, tend to preserve both radical-scavenging and cytokine suppression (Demirbağ et al., 2025).

3.2 The aldehyde is a vector, not a spectator

Unmodified vanillin already inhibits NF- κ B in colon, liver, lung, and microglia (Wu et al., 2009; Kim et al., 2019; Kafali et al., 2024). Converting the aldehyde to a carboxylic acid does not abolish this activity: vanillic acid suppresses TNF- α , IL-6, COX-2, prostaglandin E2, and nitric oxide in lipopolysaccharide-stimulated macrophages and blocks NF- κ B and caspase-1 (Kim et al., 2011). More recently, vanillic acid has been shown to limit NLRP3 inflammasome activation and gasdermin-D cleavage in acute lung injury by promoting lysosomal degradation of STIM1 and thereby lowering stimulus-evoked calcium (Wang et al., 2025). Reduction to vanillyl alcohol preserves analgesic activity in capsaicin (TRPV1) and allyl-isothiocyanate (TRPA1) tests and contributes to the resolution of carrageenan edema (Boiko et al., 2019). The medicinal chemist can therefore treat oxidation and reduction as metabolic soft spots that still yield active species, and treat condensation as the route to analogues that are no longer substrates of aldehyde dehydrogenase.

3.3 Electron-withdrawing tails and halogen patterns

Across Schiff-base, chalcone, and hybrid series, para-nitro, para-trifluoromethyl, and para-fluoro substituents recur as potency-enhancing groups when the readout is COX-2 preference, nitric-oxide suppression, or protein-denaturation protection (Suleiman et al., 2025). The chemical rationale is familiar from other COX-2 inhibitor series: an electron-deficient aryl ring improves contact with hydrophobic side pockets and can mimic the sulfonamide or methylsulfone of diarylheterocyclic coxibs without copying their exact warhead. Electron-donating para-hydroxy or para-methoxy groups are not inactive—they often retain antioxidant and moderate cytokine effects—but they less often lead the selectivity index. Ortho substitution is a steric gamble: a single ortho methoxy can help, whereas 2,6-disubstitution twists the imine or enone out of conjugation and usually costs activity.

3.4 o-Vanillin and metal coordination

Moving the hydroxyl ortho to the carbonyl creates an O,N or O,O chelator once the aldehyde is condensed with an amine. Chromium(III), iron(III), and ruthenium(III) complexes of ortho-vanillin derivatives inhibit carrageenan edema in Wistar rats at concentrations matched to diclofenac sodium (as reviewed by Kafali et al., 2024). Copper(II), nickel(II), zinc(II), and oxidovanadium(IV) complexes of an ibuprofen–o-vanillin Schiff base have been ranked for anti-inflammatory potential, with the copper complex leading, and have been docked into COX-2 (PDB 6COX). Metal coordination can therefore amplify an already anti-inflammatory ligand. It also imports a cytotoxicity and metal-accumulation problem that a chronic oral anti-inflammatory drug cannot ignore. Complexes are better read as chemical probes and topical or short-course candidates than as default systemic leads.

4. Derivative Classes and What Each Class Is For

4.1 Metabolites: vanillic acid and vanillyl alcohol

Any oral vanillin program will generate vanillic acid and, to a lesser extent, vanillyl alcohol. Bezerra-Filho and colleagues (2019) reviewed this triad specifically against inflammatory and oxidative endpoints and added a docking comparison at phospholipase A2, the enzyme that liberates arachidonic acid. The practical consequence is that a plasma assay for parent vanillin alone will understate exposure to active species. Vanillic acid is the more completely studied metabolite. In mouse peritoneal macrophages it lowers TNF- α and IL-6, suppresses COX-2 protein and prostaglandin E2, reduces nitric oxide, and interrupts NF- κ B together with caspase-1 (Kim et al., 2011). In the 2025 acute-lung-injury study, vanillic acid inhibited IL-1 β and IL-18 release from LPS-plus-nigericin-stimulated J774A.1 macrophages and, in mice, limited lung injury by a STIM1–calcium–NLRP3–gasdermin-D sequence (Wang et al., 2025). That places a vanillin metabolite on a target—NLRP3 pyroptosis—that current marketed NSAIDs do not directly address.

4.2 Schiff bases and Mannich bases

Condensation of vanillin with a primary aromatic or aliphatic amine produces the azomethine linkage that Suleiman et al. (2025) identify as a workhorse of vanillin medicinal chemistry. The imine is synthetically cheap, conjugatively planar, and hydrolytically labile enough to be discussed as a possible prodrug of vanillin plus the amine. Recent vanillin Schiff bases reduced NF- κ B, IL-6, and TNF- α protein and lowered reactive oxygen species in LPS-stimulated RAW 264.7 macrophages across the low-to-mid micromolar range, with accompanying antibacterial and acetylcholinesterase data that mark them as multi-target rather than COX-selective agents (Demirbağ et al., 2025). Mannich bases add a dialkylaminomethyl group ortho to the phenol and are used when a water-solubilizing amine is wanted without destroying the aldehyde. For anti-inflammatory design the Schiff base is the better-validated of the two.

4.3 Hydrazones

Replacement of the amine by an acid hydrazide gives an acylhydrazone. The extra carbonyl is a hydrogen-bond acceptor, and the NH is a donor, so hydrazones often dock more convincingly than simple imines into COX and LOX sites. They are also more hydrolytically stable than unsubstituted Schiff bases at gastric pH. Published vanillin hydrazones are better documented for antimicrobial, antioxidant, and anticancer endpoints than for head-to-head COX-1/COX-2 panels; where anti-inflammatory data exist, activity tracks with a free phenol and an electron-deficient aromatic hydrazide. A useful design rule is to keep the hydrazone E-configured and to avoid a second ionizable center unless a salt form is the formulation intent.

4.4 Chalcones and chalcone–acetamide hybrids

Claisen–Schmidt condensation of vanillin with a substituted acetophenone installs an α,β -unsaturated ketone. The enone is a Michael acceptor and a recognized PAINS motif; it is also the structural feature most often credited for NF- κ B and cysteine-protease engagement. Selective optimization should therefore distinguish reversible pocket binding from nonspecific thiol alkylation, using glutathione-reactivity counterscreens. Vanillin–chalcone hybrids that add an acetamide spacer have been advanced as COX-leaning anti-inflammatory series, with para-nitro and para-fluoro analogues repeatedly ranked at the top of in vitro panels and with carrageenan and cotton-pellet activity reported for the nitro lead (Suleiman et al., 2025). Until independent replication and full COX-1/COX-2 kinetics are available, these hybrids are best treated as design exemplars—evidence that an electron-deficient chalcone tail can outperform parent vanillin—rather than as clinical candidates.

4.5 Triazoles, pyrazolines, and thiadiazoles

1,4-Disubstituted 1,2,3-triazoles built from O-propargyl vanillin are metabolically robust isosteres of the imine and have been explored mainly for antimicrobial and antitubercular activity, with anti-inflammatory potential inferred from the retained guaiacol and from docking at COX and LOX (Suleiman et al., 2025; Kafali et al., 2024). Pyrazolines, formed from vanillin chalcones and hydrazine, saturate the enone and thereby reduce Michael reactivity while keeping a five-membered hydrogen-bond acceptor. Vanillin–thiadiazole hybrids have documented activity against plant pathogens and are a reminder that the same heterocycle used in carbonic-anhydrase and anti-inflammatory chemistry can be grafted onto this scaffold. For a human anti-inflammatory program, triazole and pyrazoline are the cleaner choices because they avoid the metal and the reactive enone.

4.6 Esters, ethers, and delivery constructs

Phenolic esters with NSAID acids (aspirin, ibuprofen, diclofenac) are mutual prodrugs: hydrolysis can release two anti-inflammatory species, but only if the hydrolysis rate matches the absorption window. Ethyl-vanillin and vanillin have also been built into chitosan, polyvinyl alcohol, and gelatin hydrogels for wound and burn dressings, where the anti-inflammatory contribution is local cytokine control plus antibacterial assistance (Kafali et al., 2024). Nanoparticle capping with vanillin improves colloidal stability and can concentrate the phenol at an inflamed site. These constructs do not change the intrinsic SAR; they change delivery, and they are the most direct answer to the exposure problem of the parent molecule.

Table 3. Derivative classes mapped to anti-inflammatory purpose

Class	Typical transform	What it improves	Principal risk
Vanillic acid	Aldehyde oxidation	Metabolic realism; NLRP3 / NF- κ B	Still rapidly conjugated
Vanillyl alcohol	Aldehyde reduction	TRPV1 / TRPA1 analgesia	Lower target potency than optimized imines
Schiff base	R-NH ₂ condensation	Cytokine and ROS suppression	Imine hydrolysis; aniline toxicity
Hydrazone	Hydrazide condensation	Extra H-bond pattern; stability	Sparse COX selectivity data
Chalcone hybrid	Claisen–Schmidt	Potency over parent vanillin	Enone reactivity / PAINS flag
1,2,3-Triazole	CuAAC on propargyl ether	Metabolic stability	Potency often antimicrobial-biased
Metal complex	o-Vanillin chelation	Edema potency; COX-2 docking	Metal toxicity; not for chronic oral use
Hydrogel / nano	Physical entrapment	Local exposure; wound inflammation	Not a systemic SAR solution

Note. Class purposes are interpretive and draw on Kafali et al. (2024), Suleiman et al. (2025), Bezerra-Filho et al. (2019), Demirbağ et al. (2025), Boiko et al. (2019), and Wang et al. (2025).

5. Molecular Targets and Signaling

5.1 NF- κ B as the best-validated node

The clearest mechanistic paper on parent vanillin remains the trinitrobenzene sulfonic acid colitis study of Wu et al. (2009). Oral vanillin improved macroscopic and histological colitis both preventively and therapeutically. In vivo bioluminescence, electrophoretic mobility shift, and immunoblotting showed reduced NF- κ B activity through three linked events: less I κ B kinase activation, less I κ B- α phosphorylation, and less p65 nuclear translocation. Colonic IL-1 β , IL-6, interferon- γ , and TNF- α fell, and IL-4 rose. That combination—blockade of the kinase-to-transcription sequence, not merely scavenging of a downstream mediator—is why vanillin is repeatedly described as an NF- κ B inhibitor rather than as a classical COX inhibitor (Murakami et al., 2007; Wu et al., 2009).

The same node reappears in other tissues. In LPS-stimulated BV-2 microglia, vanillin lowered nitric oxide, IL-1 β , TNF- α , and IL-6, reduced iNOS and COX-2 protein, and inhibited phosphorylation of MAPKs and NF- κ B (Kim et al., 2019). Reviews of the wider dataset extend the pattern to carbon-tetrachloride liver injury, LPS mastitis, acute lung injury, and dopaminergic neuroinflammation, with ERK1/2, p38, and AKT phosphorylation reduced alongside p65 (Kafali et al., 2024). A coherent reading is that vanillin interrupts a shared inflammatory cassette rather than a tissue-private receptor.

5.2 COX-2, prostaglandins, and the limits of direct enzyme inhibition

Murakami and colleagues (2007) re-evaluated COX-2 inhibition by vanillin and guaiacol in LPS-stimulated macrophages and cautioned against over-reading early reports of direct enzyme blockade. Vanillin does reduce COX-2 expression and prostaglandin output, but a large part of that effect is transcriptional, downstream of NF- κ B and MAPK, rather than competitive occupancy of the COX active site at nanomolar concentrations. Designed derivatives are a different case. Series that add an electron-deficient diaryl-like tail can move into the low-micromolar COX-2 range and can show selectivity indices above 20, a profile parent vanillin does not possess. Drug-development language should keep these two claims separate: the natural product is a pathway modulator; selected hybrids are enzyme inhibitors that still carry the pathway effect.

5.3 iNOS, nitric oxide, and redox coupling

Suppression of iNOS protein and of nitrite accumulation is among the most reproducible in vitro findings for vanillin, vanillic acid, and vanillin Schiff bases (Kim et al., 2011; Kim et al., 2019; Demirbağ et al., 2025). Because nitric oxide amplifies NF- κ B and damages mitochondria, iNOS suppression feeds back onto the same pathway. Parallel activation of Nrf2/HO-1, reported for vanillin in monocytic cells and summarized by Kafali et al. (2024), offers a second redox arm: induction of heme oxygenase-1 and related electrophile-response genes. Analogues that retain the free phenol are more plausible Nrf2 inducers than analogues in which the phenol is permanently capped.

5.4 NLRP3, STIM1, and pyroptosis

Inflammasome biology is the newest mechanistic layer. Vanillic acid inhibits LPS-driven STIM1 accumulation by a lysosomal-degradation route, lowers intracellular calcium, and thereby prevents NLRP3 assembly, caspase-1 cleavage, gasdermin-D cleavage, and release of IL-1 β and IL-18 (Wang et al., 2025). Parent vanillin has been reported to reduce NLRP3-associated readouts in monocytic inflammation, although the STIM1 mechanism is specifically documented for the acid. This distinction matters for analogue design. An imine that never hydrolyzes to vanillin or oxidizes to vanillic acid may keep COX affinity and lose the inflammasome effect. A prodrug designed to release vanillic acid in the lung or joint may be the more rational NLRP3 strategy.

5.5 TRP channels and the analgesic–inflammatory overlap

Boiko, Nesterkina, Shandra, and Kravchenko (2019) tested vanillin derivatives against pain evoked by the TRPV1 agonist capsaicin and the TRPA1 agonist allyl isothiocyanate, and against carrageenan edema. Vanillyl alcohol and vanillic acid shortened capsaicin-evoked licking by factors of 1.64 and 1.86, and allyl-isothiocyanate-evoked licking by factors of 1.89 and 1.74, relative to the untreated response. Anti-edema activity of the series became significant on days 2 and 3, when inflamed-paw volumes were 1.44-fold and 1.24-fold lower than control. The authors link both actions to TRPA1 and TRPV1. For drug design this is a bonus indication—analgesia accompanying inflammation control—and a warning that TRP blockade can also cause sensory adverse effects if occupancy is high.

5.6 Phospholipase A2 and upstream lipid mediators

Docking of vanillin, vanillic acid, vanillyl alcohol, and isoeugenol into a phospholipase A2 site was reported by Bezerra-Filho et al. (2019). PLA2 sits upstream of both COX and LOX, so a credible binder could, in principle, reduce prostaglandins and leukotrienes together. Docking is not inhibition. No published K_i series yet establishes vanillin derivatives as competitive PLA2 inhibitors of clinical interest. The observation is still useful as a hypothesis generator: hybrids that add a long hydrophobic tail, resembling classical PLA2 inhibitors, deserve an enzyme assay before they are interpreted solely through NF- κ B.

Table 4. Anti-inflammatory mechanisms assigned to vanillin species

Species	Best-supported nodes	Representative evidence	Design consequence
Vanillin	IKK–I κ B–p65; MAPK; iNOS; COX-2 expression	Wu et al., 2009; Kim et al., 2019	Keep a releasable guaiacol if pathway effect is desired
Vanillic acid	NF- κ B; COX-2; caspase-1; STIM1–NLRP3	Kim et al., 2011; Wang et al., 2025	Acid is a legitimate lead, not only a metabolite
Vanillyl alcohol	TRPV1 / TRPA1; edema resolution	Boiko et al., 2019	Useful analgesic metabolite; pair with anti-edema assay
Schiff bases	NF- κ B, IL-6, TNF- α , ROS in macrophages	Demirbağ et al., 2025	Confirm imine stability in acid and plasma

Species	Best-supported nodes	Representative evidence	Design consequence
Chalcone hybrids	COX-2-leaning inhibition; NO; edema	Suleiman et al., 2025	Counterscreen for thiol reactivity
o-Vanillin complexes	Carrageenan edema; COX-2 docking	Kafali et al., 2024	Restrict to topical or probe use pending metal safety

6. Preclinical Evidence, Organized by Model

6.1 Macrophage and monocyte assays

LPS-stimulated RAW 264.7, J774A.1, THP-1, and primary peritoneal macrophages are the workhorse assays. Endpoints that move together—nitrite, TNF- α , IL-6, IL-1 β , COX-2 protein, prostaglandin E2—are more convincing than any single ELISA. Vanillic acid covers this panel in primary mouse macrophages and adds caspase-1 (Kim et al., 2011). Vanillin covers it in BV-2 microglia with MAPK and NF- κ B phosphorylation as mechanistic anchors (Kim et al., 2019). Vanillin Schiff bases cover NF- κ B, IL-6, TNF- α , and ROS in RAW 264.7 cells (Demirbağ et al., 2025). A development series should report all four mediators plus viability, because an apparent cytokine drop that tracks loss of cell number is cytotoxicity, not anti-inflammatory activity.

6.2 Carrageenan paw edema and related acute models

Carrageenan edema has an early histamine–serotonin phase and a later prostaglandin phase. Parent vanillin at 100 and 200 mg/kg reduces rat paw volume, with the 200 mg/kg dose active across both phases and the 100 mg/kg dose clearer after the second hour; 10 mg/kg is ineffective in that dataset. Aspirin at 400 mg/kg was the reference anti-inflammatory control. The implication is dose-dependence and a bias toward the prostaglandin phase, which fits a transcriptional COX-2 effect better than a mast-cell effect. Boiko et al. (2019) similarly found that vanillin-derivative ointments separated from control on days 2 and 3 rather than on day 1, and that vanillin, vanillic acid, and vanillyl alcohol did not differ greatly from one another once the effect appeared. Delayed onset should be written into clinical-study design: a single-dose dental-pain model may underestimate this scaffold.

6.3 Colitis and barrier inflammation

TNBS colitis is the landmark *in vivo* model for vanillin. Benefit was dose-dependent, present when vanillin was given before or after the hapten, and mechanistically tied to NF- κ B (Wu et al., 2009). Later work on azoxymethane/dextran sulfate sodium colorectal carcinogenesis found that vanillin downregulates proteasome, NF- κ B, and MAPK signaling in the inflamed colon, connecting anti-inflammatory action to a reduction in inflammation-associated tumor promotion (Li et al., 2018; Kafali et al., 2024). For analogue design, colitis is the right efficacy gate for any derivative claimed to improve on oral vanillin: the parent already works, so the analogue must win on dose, on histological score, or on safety, not merely on a biochemical surrogate.

6.4 Lung, liver, and neuroinflammation

Acute lung injury condenses the case for vanillic acid. Inhibition of STIM1, NLRP3, and gasdermin-D-linked pyroptosis is a mechanism with a clear tissue readout—less lung injury—and a clear biomarker set (IL-1 β , IL-18, cleaved caspase-1, cleaved gasdermin-D) that can be carried into analogue screening (Wang et al., 2025). Hepatoprotection against carbon tetrachloride has been attributed to lower TNF- α , IL-1 β , IL-6, and COX-2 together with lower transaminases, and is summarized in the critical review literature (Kafali et al., 2024). Microglial work positions vanillin as a candidate adjunct in neuroinflammatory states, with the usual caveat that brain exposure of a conjugated phenol is limited unless a prodrug or intranasal formulation is used (Kim et al., 2019).

6.5 Wound and cutaneous inflammation

Zinc–vanillin complexes and ethyl-vanillin hydrogels increase VEGF and TGF- β and decrease TNF- α and IL-1 β in diabetic-wound and dressing models, as assembled by Kafali et al. (2024). Cutaneous delivery sidesteps first-pass conjugation. It is the indication in which a metal complex or a high local concentration is easiest to justify, and in which antibacterial activity of the same molecule becomes an asset rather than a distraction.

Table 5. Selected *in vivo* anti-inflammatory findings for vanillin and close analogues

Model	Agent and dose context	Principal result	Source
TNBS colitis, mouse	Oral vanillin, preventive and therapeutic	Improved macroscopy and histology; less p65 translocation; less IL-1 β , IL-6, IFN- γ , TNF- α ; more IL-4	Wu et al., 2009
Carrageenan edema, rat	Vanillin 100 and 200 mg/kg; 10 mg/kg inactive	Lower paw volume; 200 mg/kg active on early and late phases	Paw-edema evaluations; see also Boiko et al., 2019

Model	Agent and dose context	Principal result	Source
Carrageenan edema, derivative ointments	Vanillin, vanillic acid, vanillyl alcohol	Day-2 and day-3 volumes 1.44× and 1.24× below control	Boiko et al., 2019
Capsaicin and AITC pain	Vanillyl alcohol; vanillic acid	Licking reduced 1.64–1.89× (alcohol) and 1.74–1.86× (acid)	Boiko et al., 2019
LPS acute lung injury	Vanillic acid	Less IL-1 β /IL-18; STIM1 degradation; less NLRP3–GSDMD pyroptosis	Wang et al., 2025
AOM/DSS colon	Vanillin	Proteasome, NF- κ B, and MAPK downregulation	Li et al., 2018
o-Vanillin metal complexes	Matched to diclofenac in carrageenan test	Edema inhibition by Cr(III), Fe(III), Ru(III) complexes	Reviewed in Kafali et al., 2024

Note. Fold changes are those stated by Boiko et al. (2019). Other rows summarize direction of effect. Exact milligram-per-kilogram values should be confirmed in the primary tables before citation in a submitted paper.

Table 6. In vitro cellular signatures useful as a screening cascade

Tier	Assay	Advance criterion	Fail criterion
1. Safety	RAW 264.7 or THP-1 viability, 24 h	IC ₅₀ viability at least 10× above active concentration	Cytokine drop explained by cell loss
2. Mediators	Nitrite, TNF- α , IL-6, PGE ₂	≥50% suppression without viability loss	Only one mediator moves
3. Pathway	p-p65, p-I κ B α , p-p38, iNOS, COX-2	Concordant reduction of at least two nodes	Protein change without mRNA or vice versa only
4. Selectivity	COX-1, COX-2, 5-LOX enzyme assays	COX-2 IC ₅₀ < 5 μ M and SI > 10, or a stated multi-target rationale	SI < 2 with no pathway benefit
5. Inflammasome	LPS + nigericin IL-1 β ; cleaved GSDMD	Suppression if NLRP3 claim is made	Claim based on docking alone
6. Developability	Solubility, microsomal t _{1/2} , GSH reactivity	t _{1/2} > 30 min; low GSH adduct if enone present	Enone series with high thiol trapping

Note. Thresholds are proposed development gates for this scaffold, informed by the assays used in Kim et al. (2011), Kim et al. (2019), Demirbağ et al. (2025), and Wang et al. (2025). They are not regulatory criteria.

7. Comparative Pharmacology: Parent, Metabolite, and Designed Analogue

A recurring error in natural-product papers is to declare a derivative “more active than the standard drug” on a single percent-inhibition number at a single concentration. For vanillin the fair comparison has three arms: parent, metabolite, and analogue, each against a named standard, each at a concentration or dose justified by exposure. Parent vanillin is reproducibly active in vivo but requires high milligram-per-kilogram doses and acts with a lag. Vanillic acid matches or exceeds the parent on macrophage and lung endpoints and adds an inflammasome mechanism the parent literature does not fully own. Designed Schiff bases and chalcone hybrids can beat the parent on in vitro potency and, in some edema models, on percent inhibition at a lower dose. They have not yet beaten the parent on the quality of mechanistic evidence.

Standards should be matched to the claim. Indomethacin and diclofenac are appropriate for edema and COX assays. Dexamethasone is appropriate for cytokine and NF- κ B assays. A selective NLRP3 inhibitor, where available, is the right control for pyroptosis claims. Comparing a 20 mg/kg hybrid only with indomethacin, and not with vanillin at the same dose, leaves the central SAR question unanswered: did the structural change help? Boiko et al. (2019) are exemplary on this point because vanillin, vanillic acid, and vanillyl alcohol were run side by side.

Table 7. How to read activity claims for this scaffold

Claim type	Minimum evidence	Common over-read	Preferred wording
“More potent than vanillin”	Same assay, same lab, concentration–response	Single-dose percent vs literature vanillin	“X-fold lower IC ₅₀ than vanillin in this assay”

Claim type	Minimum evidence	Common over-read	Preferred wording
“COX-2 selective”	Both isoforms, SI reported, n stated	COX-2 only, or SI from one point	“SI = COX-1 IC50 / COX-2 IC50”
“Superior to indomethacin”	Same model, equimolar or exposure-matched	Lower dose, different vehicle, n = 3	“Percent inhibition at the tested dose”
“NF-κB inhibitor”	p65 translocation or IκB phosphorylation	A cytokine decrease alone	“Consistent with NF-κB pathway suppression”
“NLRP3 inhibitor”	ASC speck or cleaved caspase-1 plus IL-1β	IL-1β ELISA only	“Reduces NLRP3-dependent IL-1β”
“Drug-like”	Rule-of-five plus stability and Ames or micronucleus	Docking score and LogP only	“Orally plausible; safety package incomplete”

8. Pharmacokinetics, Metabolism, and Formulation

8.1 What is known

Vanillin is absorbed after oral administration and undergoes rapid phase-I oxidation to vanillic acid and phase-II conjugation. Vanillyl alcohol is a reductive metabolite of smaller quantitative importance. Because both oxidation and reduction products are active, metabolite exposure is part of the pharmacology, not only part of the clearance (Bezerra-Filho et al., 2019; Wang et al., 2025). Published human pharmacokinetic series are limited; flavor exposure is not a substitute for therapeutic-dose kinetics. A development program should quantify parent, vanillic acid, vanillyl alcohol, and the principal glucuronides in plasma and urine, and should test whether an imine or ester survives the gut long enough to be absorbed intact.

8.2 Formulation answers already in the literature

Three formulation logics are already visible. First, topical hydrogels and films of vanillin or ethyl vanillin with chitosan, gelatin, or polyvinyl alcohol deliver a high local concentration to inflamed or wounded skin and add antibacterial surface activity (Kafali et al., 2024). Second, phenolic ester mutual prodrugs with an NSAID acid aim to release two actives after absorption. Third, vanillin-capped or vanillin-loaded nanoparticles are justified when the goal is stability and residence rather than a new mechanism. Intranasal or lipid-carrier approaches, familiar from other polar neuroprotective phenols, are a logical but still largely untested route if the indication is microglial inflammation.

8.3 ADME flags by chemotype

Schiff bases must be checked for acid hydrolysis; a compound that is only an imine in the NMR tube and only vanillin in the stomach should be labeled a prodrug. Chalcones must be checked for glutathione trapping. Metal complexes must be checked for metal release in serum. Triazoles are the least worrying on metabolism and the most in need of potency optimization. Vanillic acid is the least worrying on safety precedent and the most in need of a half-life extension, for example by a hydrolyzable ester that still feeds the STIM1–NLRP3 mechanism.

Table 8. Developability snapshot by chemotype

Chemotype	Oral plausibility	Metabolic soft spot	Formulation priority	First safety screen
Vanillin	Moderate; high dose	Phenol conjugation; aldehyde oxidation	Ester prodrug or local gel	Genotoxicity of aldehyde at high dose
Vanillic acid	Moderate	Glucuronidation	Ester or lung-targeted particle	Standard phenolic package
Schiff base	Uncertain	Imine hydrolysis; aniline release	Enteric coat if prodrug	Aniline / Ames
Chalcone	Low to moderate	Michael addition to GSH	Only if GSH-stable	Thiol reactivity; hERG if basic
Triazole	Good	Slow oxidation of methoxy	Conventional oral	CYP panel
Metal complex	Poor for chronic use	Ligand exchange	Topical only at first	Metal biodistribution

Note. Ratings are medicinal-chemistry judgments based on functional-group precedent and on the formulation discussion in Kafali et al. (2024) and Suleiman et al. (2025), not on a completed regulatory package.

9. Safety, Selectivity, and the Case Against Over-Claiming

Food use of vanillin is reassuring at flavor doses and is not a carcinogenicity or reproductive waiver at

pharmacological doses. The aldehyde can form Schiff bases with protein lysines; at high concentration that is a haptenation risk. Electron-deficient anilines released from hydrolyzed Schiff bases carry their own genotoxic precedent and should be avoided or justified with negative Ames and micronucleus data. Metal complexes that match diclofenac in a paw-edema test have not been shown to match diclofenac's therapeutic index, and diclofenac's index is itself limited.

Selectivity is the other safety issue. An analogue that inhibits COX-1 and COX-2 equally will inherit NSAID gastrointestinal risk no matter how natural its starting material. An analogue that covalently modifies many cysteines will look potent in every NF- κ B assay and fail in every off-target panel. The SAR recommendation that follows is deliberate: prefer reversible binders with a measured COX-2 selectivity index, keep a free or releasable phenol if Nrf2 contribution is wanted, and treat enones and metal centers as conditional tools.

Drug–drug interaction potential is largely unstudied. Phenolic conjugation can theoretically compete with other glucuronidated drugs, and any new basic side chain introduced by a Mannich or acetamide hybrid needs a CYP and transporter screen. None of the published anti-inflammatory series reviewed here includes a clinical drug–drug interaction assessment.

10. Advancements in Anti-Inflammatory Drug Development

10.1 What has actually advanced

Advancement on this scaffold is real but preclinical. Relative to 2009, when Wu and colleagues established NF- κ B-dependent colitis control, the field now has (i) a metabolite, vanillic acid, with a defined inflammasome mechanism in lung injury; (ii) a TRP-linked analgesic SAR for the alcohol and the acid; (iii) Schiff bases with macrophage cytokine data; (iv) a synthetic map of hotspots and routes covering 2014–2025; and (v) formulation prototypes for skin (Kafali et al., 2024; Suleiman et al., 2025; Wang et al., 2025; Boiko et al., 2019; Demirbağ et al., 2025). No vanillin derivative is an approved anti-inflammatory medicine. That sentence should stay in the abstract of any paper that uses the word “advancement.”

10.2 A practical design cycle

A productive next cycle is narrow. Start with vanillin or vanillic acid, not with a metal. Install one of three tails: a hydrolytically characterized acylhydrazone, a GSH-stable pyrazoline derived from a chalcone, or a 1,2,3-triazole. Keep the C4 phenol free. Use para-fluoro or para-trifluoromethyl rather than para-nitro if aniline or nitro reduction is a concern, accepting that nitro may win the first enzyme assay. Measure COX-1, COX-2, 5-LOX, nitrite, TNF- α , and IL-1 β after nigericin. Advance only compounds that beat vanillin by at least threefold on two endpoints and that do not lose the NF- κ B signature. Take two compounds, not ten, into carrageenan edema and into either TNBS colitis or LPS lung injury, with vanillic acid as the internal control.

10.3 Indication matching

Indication should follow mechanism. Colitis and inflammation-associated colon risk match the strongest parent dataset (Wu et al., 2009; Li et al., 2018). Acute lung injury and inflammasome-high pulmonary inflammation match vanillic acid (Wang et al., 2025). Osteoarthritis and other prostaglandin-high joint diseases match COX-leaning hybrids, but only after selectivity is shown. Neuroinflammation matches the BV-2 mechanism (Kim et al., 2019) and almost certainly requires a formulation solution. Diabetic wounds match gels and zinc complexes already explored in preclinical dressings (Kafali et al., 2024). A single “anti-inflammatory vanillin derivative” aimed at all of these indications will not be developable.

Table 9. Indication-to-chemotype matching

Indication	Why this scaffold fits	Preferred chemotype	Key experiment still missing
Inflammatory bowel disease	Oral vanillin already active via NF- κ B	Stable hydrazone or triazole prodrug of vanillin	Head-to-head vs vanillin on histology
Acute lung injury	Vanillic acid blocks STIM1–NLRP3–GSDMD	Lung-retained vanillic acid ester	Inhaled PK and STIM1 confirmation
Osteoarthritis pain	Edema plus TRPV1/TRPA1 activity	COX-2-selective non-enone hybrid	Cartilage explant and selectivity panel
Neuroinflammation	Microglial MAPK / NF- κ B suppression	Lipophilic prodrug of vanillin or acid	Brain unbound concentration
Diabetic wound	Local cytokine shift; dressing data exist	Vanillin hydrogel; avoid systemic metal	Controlled clinical dressing study
Inflammation-associated CRC risk	AOM/DSS pathway data	Oral vanillin analogue with colon exposure	Long-term tumor-multiplicity study

11. Gaps, Contradictions, and Research Agenda

Several gaps are large enough to shape the next paper rather than to decorate its conclusion. Human pharmacokinetics at pharmacological doses are not established. Direct COX-2 Ki values for parent vanillin are modest or inconsistent, and papers still slide from “reduces COX-2 expression” to “COX-2 inhibitor.” Enantiomerically pure series do not exist because the parent is achiral, but several hybrids introduce stereocenters and are tested as racemates. Female animals, aged animals, and comorbid metabolic models are underrepresented relative to young male rats. Replication across laboratories is thin: the TNBS result, the BV-2 result, and the STIM1 result each need an independent confirmation before a lead is nominated.

There is also a literature-quality gap. Some derivative papers report striking IC50 and selectivity values from single laboratories without a deposited spectral archive or a COX enzyme lot number. Until those numbers are reproduced, SAR tables in a review should mark them as provisional. The present review therefore uses such series as illustrations of substituent trends, not as potency standards.

The research agenda that follows is short. Publish full concentration–response curves against vanillin and vanillic acid in the same plate. Deposit NMR and HRMS. Run COX-1 and COX-2 with a reference coxib. Add a glutathione-reactivity number for every enone. Measure STIM1 and cleaved gasdermin-D if the claim mentions inflammasomes. Report the day-2 as well as the hour-4 edema result, because this scaffold’s *in vivo* signature is delayed. Those six habits would raise the signal of the field more than another twenty unbenchmarked analogues.

12. Conclusion

Vanillin is a small phenolic aldehyde with a disproportionately useful anti-inflammatory pharmacology. The parent molecule suppresses the IKK–I κ B–p65 sequence, damps MAPK phosphorylation, and lowers iNOS, COX-2 expression, and the cytokines that those transcription factors control. Its acid metabolite extends the mechanism to STIM1-dependent NLRP3 inflammasome activation and pyroptosis. Its alcohol metabolite preserves TRP-linked analgesia. Designed derivatives—Schiff bases, hydrazones, chalcone hybrids, triazoles, and ortho-vanillin metal complexes—show that the aldehyde and the ortho-hydroxy isomer are productive SAR hotspots, and that electron-withdrawing aryl tails can push activity beyond the parent in enzyme and edema assays.

The advancement is therefore best described as platform building, not as a finished drug class. The scaffold is cheap, synthetically open, and mechanistically broader than a classical NSAID. It is also under-optimized on selectivity, exposure, and independent replication. The rational next analogues will keep a free or releasable guaiacol phenol, replace the metabolically soft aldehyde with a characterized hydrazone, pyrazoline, or triazole, avoid unnecessary nitroanilines and chronic metal centers, and be judged against vanillin and vanillic acid rather than only against indomethacin. Used that way, vanillin derivatives are a credible route to multi-pathway anti-inflammatory leads for colitis, inflammasome-high lung injury, and local cutaneous inflammation.

References

1. JBezerra-Filho, C. S. M., Barboza, J. N., Souza, M. T. S., & Sabry, P. (2019). Therapeutic potential of vanillin and its main metabolites to regulate the inflammatory response and oxidative stress. *Mini Reviews in Medicinal Chemistry*, 19(20), 1681–1693. <https://doi.org/10.2174/1389557519666190312164355>
2. Boiko, Y. A., Nesterkina, M. V., Shandra, A. A., & Kravchenko, I. A. (2019). Analgesic and anti-inflammatory activity of vanillin derivatives. *Pharmaceutical Chemistry Journal*, 53(7), 650–654. <https://doi.org/10.1007/s11094-019-02056-2>
3. Demirbağ, B., Yildirim, M., Cimentepe, M., Necip, A., Unver, H., & Tiftik, E. N. (2025). Novel vanillin-derived Schiff bases: Synthesis, characterization, antibacterial activity, enzyme inhibition, antioxidant activity, anti-inflammatory activity on LPS-induced RAW 264.7 macrophage cell line, and *in silico* studies. *Journal of Molecular Structure*, 1338, Article 142320. <https://doi.org/10.1016/j.molstruc.2025.142320>
4. Kafali, M., Finos, M. A., & Tsoupras, A. (2024). Vanillin and its derivatives: A critical review of their anti-inflammatory, anti-infective, wound-healing, neuroprotective, and anti-cancer health-promoting benefits. *Nutraceuticals*, 4(4), 522–561. <https://doi.org/10.3390/nutraceuticals4040030>
5. Kim, M.-C., Kim, S.-J., & Kim, D.-S. (2011). Vanillic acid inhibits inflammatory mediators by suppressing NF- κ B in lipopolysaccharide-stimulated mouse peritoneal macrophages. *Immunopharmacology and Immunotoxicology*, 33(3), 525–532. <https://doi.org/10.3109/08923973.2010.547500>
6. Kim, M. E., Na, J. Y., & Lee, J. S. (2019). Anti-neuroinflammatory effects of vanillin through the regulation of inflammatory factors and NF- κ B signaling in LPS-stimulated microglia. *Applied Biochemistry and Biotechnology*, 187(3), 884–893. <https://doi.org/10.1007/s12010-018-2857-5>
7. Li, J.-M., Lee, Y.-C., Li, C.-C., Lo, H.-Y., Chen, F.-Y., Chen, Y.-S., Hsiang, C.-Y., & Ho, T.-Y. (2018). Vanillin-ameliorated development of azoxymethane/dextran sodium sulfate-induced murine colorectal cancer: The involvement of proteasome/nuclear factor- κ B/mitogen-activated protein kinase pathways. *Journal of Agricultural and Food Chemistry*, 66(22), 5563–5573. <https://doi.org/10.1021/acs.jafc.8b01582>
8. Murakami, Y., Hirata, A., Ito, S., Shoji, M., Tanaka, S., Yasui, T., Machino, M., & Fujisawa, S. (2007). Re-evaluation of cyclooxygenase-2-inhibiting activity of vanillin and guaiacol in macrophages stimulated with lipopolysaccharide. *Anticancer Research*, 27(2), 801–808.
9. Suleiman, M., Sankaranarayanan, M., Theva Das, K., Amran, S. I., Berezin, V., Andrey, B., & Jamalis, J. (2025). Vanillin derivatives in drug design: Structure–activity relationship (SAR) hotspots and synthetic pathways for enhanced pharmacological activity. *ACS Omega*, 10(48), 57846–57875. <https://doi.org/10.1021/acsomega.5c02176>

10. Wang, L., Li, H.-D., Sun, X., Ni, J.-H., Feng, G.-Z., Shen, X.-Y., Weng, H.-B., & Fang, H. (2025). The protective effects of vanillic acid on LPS-induced acute lung injury by inhibiting STIM1-mediated NLRP3 inflammasome activation. *Inflammation*, 48, 3710–3725. <https://doi.org/10.1007/s10753-025-02293-6>
11. Wu, S.-L., Chen, J.-C., Li, C.-C., Lo, H.-Y., Ho, T.-Y., & Hsiang, C.-Y. (2009). Vanillin improves and prevents trinitrobenzene sulfonic acid-induced colitis in mice. *The Journal of Pharmacology and Experimental Therapeutics*, 330(2), 370–376. <https://doi.org/10.1124/jpet.109.152835>

Appendix A. Glossary of Abbreviations

AOM/DSS - Azoxymethane / dextran sodium sulfate, a colitis-associated cancer model
COX-1 / COX-2 — Cyclooxygenase isoforms 1 and 2
GSDMD — Gasdermin D, the pyroptosis executioner cleaved downstream of caspase-1
IKK — I κ B kinase, the kinase complex that marks I κ B for degradation
iNOS — Inducible nitric oxide synthase
MAPK — Mitogen-activated protein kinase (ERK1/2, JNK, p38)
NF- κ B — Nuclear factor kappa B; p65 is the RelA subunit
NLRP3 — NOD-like receptor family pyrin domain-containing 3 inflammasome
Nrf2/HO-1 — Nuclear factor erythroid 2-related factor 2 / heme oxygenase-1 axis
PLA2 — Phospholipase A2
SAR — Structure–activity relationship
STIM1 — Stromal interaction molecule 1, a calcium-store sensor
TNBS — Trinitrobenzene sulfonic acid
TRPA1 / TRPV1 — Transient receptor potential ankyrin 1 and vanilloid 1 channels