

RESEARCH MONOGRAPH . COMPOUND PROFILE

Apigenin

A dietary flavone abundant in chamomile, parsley, and celery, distinguished from other common flavonoids by potent CD38 NADase inhibition with consequent elevation of intracellular NAD⁺, moderate GABA-A receptor activity at the benzodiazepine site, competitive aromatase inhibition, and a broad preclinical pharmacology spanning anti-inflammatory, neuroprotective, anti-cancer, and metabolic endpoints.

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ABSTRACT

Apigenin (4',5,7-trihydroxyflavone) is a naturally occurring flavone present at high concentration in chamomile flowers, parsley, celery, and numerous other dietary plant sources. It is one of the most extensively studied plant flavonoids, with a preclinical research literature encompassing anti-inflammatory, antioxidant, neuroprotective, anxiolytic, anti-cancer, cardioprotective, and metabolic activities. The compound is distinguished from the structurally related flavonoids quercetin, luteolin, and kaempferol by several pharmacological features of particular current research interest: potent inhibition of CD38, the principal mammalian NAD⁺-degrading ectoenzyme, resulting in elevation of intracellular nicotinamide adenine dinucleotide (NAD⁺) and consequent activation of sirtuin-dependent deacetylation pathways relevant to metabolic syndrome and aging; moderate activity at the benzodiazepine binding site of the gamma-aminobutyric acid type A (GABA-A) receptor, producing anxiolytic and sedative effects in rodent models; competitive inhibition of aromatase (CYP19A1) with an IC₅₀ of approximately 20 to 23 micromolar, reducing estrogen biosynthesis; and suppression of NF-kappaB-driven proinflammatory cytokine production through multiple converging mechanisms including direct IKK-beta inhibition and modulation of the PI3K/AKT and MAPK/ERK signaling cascades.

The CD38 inhibitory activity, formally characterized by Escande et al. (2013) in a report from the Bhatt, Chini, and Sinclair laboratories, demonstrated that apigenin administration to obese mice increased tissue NAD⁺ levels, decreased global protein

acetylation through sirtuin activation, and improved glucose and lipid homeostasis parameters [1]. This finding positioned apigenin within the NAD⁺ restoration research framework alongside nicotinamide mononucleotide and nicotinamide riboside, though through a mechanistically distinct pathway (reduced NAD⁺ degradation rather than precursor supplementation). The GABA-A receptor activity, first reported by Viola et al. (1995) using competitive radioligand displacement at the benzodiazepine site, produced anxiolytic effects in elevated plus maze and open field paradigms in mice without the sedation, amnesia, or muscle relaxation characteristic of classical benzodiazepines [2]. Subsequent electrophysiological and behavioral studies have produced conflicting characterizations of the precise nature of the GABA-A interaction, with reports variously describing apigenin as a weak partial agonist, an antagonist, or an inverse agonist at the benzodiazepine site depending on assay system and concentration.

Pharmacokinetics in humans are incompletely characterized. Oral bioavailability is estimated at approximately 30 percent, limited by poor aqueous solubility and extensive first-pass phase II conjugation (glucuronidation and sulfation). Phase I oxidative metabolism is mediated principally by CYP1A1, CYP1A2, and CYP2E1, producing the hydroxylated metabolite luteolin as the major oxidative product. The plasma elimination half-life after oral administration is approximately 2 to 3 hours in the limited human pharmacokinetic data available. Apigenin inhibits CYP2C9, CYP3A4, and P-glycoprotein in vitro at concentrations that may be clinically relevant at supplemental doses, raising drug-drug interaction considerations.

The compound is non-mutagenic and non-genotoxic in standard regulatory toxicology assays. No significant toxicity has been observed in animal studies at doses up to 50 mg/kg, though hepatotoxicity has been reported at intraperitoneal doses of 100 mg/kg and above in mice. Human safety data at supplemental doses (50 to 500 mg daily) are limited but have not produced serious adverse event signals. The principal reported adverse effects at supplemental doses are drowsiness (consistent with GABA-A activity) and mild gastrointestinal discomfort.

This monograph reviews the chemistry, natural sources, and isolation history of apigenin; the multi-target molecular pharmacology spanning CD38, GABA-A, aromatase, and inflammatory signaling; the available pharmacokinetic data in animals and humans; the preclinical pharmacology across neuroprotective, anti-cancer, anti-inflammatory, and metabolic endpoints; the limited clinical evidence base; sourcing and quality verification for research applications; reconstitution and handling; stack interactions; adverse events and safety; and a comparative assessment of five structurally or functionally related flavonoid compounds against apigenin on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Apigenin (not assigned a formal INN; the compound is a dietary flavonoid rather than a registered pharmaceutical).

Common names and synonyms: Apigenin, 4',5,7-trihydroxyflavone, 5,7-dihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one, apigenol, chamomile flavone, C.I. Natural Yellow 1.

Chemical Abstracts Service registry number: 520-36-5.

PubChem CID: 5280443.

International Union of Pure and Applied Chemistry name: 5,7-dihydroxy-2-(4-hydroxyphenyl)chromen-4-one. The compound is the parent aglycone of a family of naturally occurring glycosides including apiin (apigenin 7-O-apioglucoside), vitexin (apigenin 8-C-glucoside), isovitexin (apigenin 6-C-glucoside), apigetrin (apigenin 7-O-glucoside), and cosmosiin (apigenin 7-O-glucoside, also identified as apigetrin in some nomenclature systems).

1.2 Structural class and chemistry

Apigenin belongs to the flavone subclass of the flavonoid family, a large group of polyphenolic plant secondary metabolites characterized by the 2-phenylchromen-4-one (flavone) backbone. Within the flavone subclass, apigenin is the simplest trihydroxyflavone, bearing hydroxyl groups at the 4', 5, and 7 positions. The structural class places it in close relationship to luteolin (3',4',5,7-tetrahydroxyflavone, differing by one additional hydroxyl at the 3' position of the B-ring), chrysin (5,7-dihydroxyflavone, lacking the 4'-hydroxyl), and baicalein (5,6,7-trihydroxyflavone, with the third hydroxyl at the 6 rather than 4' position) [3].

Molecular formula: C₁₅H₁₀O₅.

Exact mass: 270.0528 g/mol (monoisotopic).

Molecular weight: 270.24 g/mol.

Physical properties: Yellow crystalline powder. Poorly soluble in water (approximately 2.16 micrograms per milliliter at 25 degrees Celsius), soluble in dimethyl sulfoxide and in dilute alkali solutions. Melting point is reported as 345 to 350 degrees Celsius (with decomposition). The compound is stable under standard storage conditions and does not contain chiral centers; it is achiral and is supplied as a single stereochemically defined entity.

Stereochemistry: Apigenin has no stereocenters and no geometric isomerism. The compound is planar, with the B-ring and the chromenone A/C-ring system approximately coplanar in the crystalline state. The planarity is important for receptor binding interactions, particularly at the benzodiazepine site of the GABA-A receptor and at the active site of aromatase (CYP19A1), where the flat flavone scaffold occupies the substrate-binding channel.

1.3 Biosynthesis and isolation

Apigenin is biosynthesized in plants through the phenylpropanoid and flavonoid pathways. The immediate biosynthetic precursor is the flavanone naringenin, which is oxidized to apigenin by flavone synthase (FNS I or FNS II depending on the plant species) [4]. The biosynthetic pathway proceeds from phenylalanine through cinnamate, 4-coumaroyl-CoA, naringenin chalcone, naringenin, and finally apigenin.

Isolation from plant material is typically accomplished by extraction of dried plant material (chamomile flowers, parsley leaves, or celery seeds) with ethanol, methanol, or ethanol-water mixtures, followed by liquid-liquid partitioning, silica gel column chromatography, and preparative high-performance liquid chromatography [5]. The aglycone may also be obtained by acid hydrolysis of the glycosides (apiin, vitexin, isovitexin) present in the plant extract. Modern commercial production uses either extraction from chamomile flowers or celery seeds at scale, or total chemical synthesis from phloroglucinol and 4-hydroxybenzaldehyde derivatives through chalcone cyclization.

Research-grade and supplement-grade apigenin is supplied by multiple manufacturers at purities of 95 to 98 percent or greater by HPLC, typically as the free aglycone.

2. Abstract

Apigenin (4',5,7-trihydroxyflavone, CAS 520-36-5) is a plant-derived flavone with a broad multi-target pharmacology that spans enzymatic inhibition, receptor modulation, and intracellular signaling pathway regulation. The compound has attracted sustained research interest across multiple therapeutic domains, principally on the strength of four molecular activities characterized at pharmacologically relevant concentrations: inhibition of the ectoenzyme CD38 (the dominant mammalian NADase), resulting in preservation and elevation of intracellular NAD⁺ and consequent sirtuin pathway activation [1]; modulation of the GABA-A receptor at the benzodiazepine binding site, producing anxiolytic effects in animal models [2]; competitive inhibition of aromatase (CYP19A1), reducing androgen-to-estrogen conversion [6]; and suppression of NF-kappaB-driven inflammatory gene transcription through direct and indirect mechanisms [7].

The CD38 inhibitory activity is the molecular basis for the current positioning of apigenin within the NAD⁺ restoration and longevity research space. Escande et al. (2013) demonstrated that apigenin increases intracellular NAD⁺ in wild-type but not in CD38 knockout cells, confirming that the NAD⁺ effect is mediated through CD38 inhibition rather than through alternative pathways [1]. In diet-induced obese mice, apigenin treatment elevated tissue NAD⁺ levels, decreased global protein acetylation (a surrogate for sirtuin activation), and improved glucose tolerance and lipid profiles. These findings have positioned apigenin as a mechanistically complementary agent to NAD⁺ precursor supplementation (nicotinamide mononucleotide, nicotinamide riboside), acting on the degradation rather than the synthesis arm of the NAD⁺ metabolic cycle.

The GABA-A receptor activity, characterized by Viola et al. (1995) using [3H]flumazenil displacement in rat cerebellar membranes (IC₅₀ approximately 250 micromolar) and behavioral anxiolytic assays in mice at intraperitoneal doses of 1 to 3 mg/kg [2], has been the basis for the traditional association of chamomile tea consumption with relaxation and sleep promotion. Subsequent reports have produced divergent pharmacological characterizations (partial agonist, antagonist, inverse agonist) depending on the receptor subunit composition and assay system, indicating that the GABA-A interaction is complex and may involve both benzodiazepine-site-dependent and benzodiazepine-site-independent components [8, 9].

The preclinical pharmacology of apigenin is extensive. In cancer models, the compound suppresses proliferation and induces apoptosis in cell lines derived from breast, prostate, lung, colon, liver, pancreatic, and hematologic malignancies, with in vivo tumor suppression demonstrated at oral doses of 20 to 50 micrograms per mouse per day in xenograft and transgenic models [10, 11]. In neuroprotection models, apigenin crosses the blood-brain barrier and produces cognitive improvement, reduced amyloid-beta deposition, attenuated tau hyperphosphorylation, and microglial anti-inflammatory polarization in rodent models of Alzheimer's disease, Parkinson's disease, and excitotoxic injury [12, 13]. In metabolic models, the CD38-NAD⁺-sirtuin axis underpins improvements in insulin sensitivity, hepatic lipid metabolism, and mitochondrial function [1].

The clinical evidence base for apigenin as an isolated compound is limited. Most human evidence derives from studies of chamomile extract (which contains apigenin as an active constituent alongside other flavonoids and terpenoids) for anxiety, insomnia, and general well-being endpoints. A small number of human pharmacokinetic studies have been conducted with defined apigenin doses. No registration trial for any indication has been completed with purified apigenin. The compound is commercially available as a dietary supplement in the United States at doses of 50 to 500 mg and as a research-grade chemical at purities exceeding 98 percent.

3. Discovery and Development History

3.1 Isolation and early chemistry

Apigenin was first isolated from parsley (*Petroselinum crispum*) by Rump in the mid-nineteenth century, extracted from parsley seeds by treatment with boiling water to produce a gelatinous precipitate that was subsequently characterized as a glycoside. The aglycone apigenin was obtained by acid hydrolysis of the glycoside fraction. Independent isolation from chamomile (*Matricaria chamomilla*, now *Matricaria recutita*) flowers was reported in 1914 [5]. The chemical structure was established as 4',5,7-trihydroxyflavone through classical degradative chemistry and was confirmed by total synthesis in the early twentieth century.

3.2 Identification of biological activities

The pharmacological characterization of apigenin proceeded in several waves. The anti-inflammatory and antioxidant activities were recognized in the 1970s and 1980s as part of the broader investigation of dietary flavonoids as modulators of eicosanoid metabolism and reactive oxygen species [3]. The GABA-A receptor interaction was formally characterized by Viola et al. in 1995, establishing apigenin as a ligand at the benzodiazepine binding site with anxiolytic properties in mice [2]. This report catalyzed interest in the neuropsychiatric pharmacology of dietary flavones and provided a molecular rationale for the traditional use of chamomile preparations for anxiety and sleep.

3.3 CD38 inhibition and the NAD⁺ connection

The identification of apigenin as a CD38 inhibitor by Escande et al. (2013) at the Mayo Clinic, Harvard Medical School, and associated laboratories represented a significant expansion of the compound's research profile [1]. CD38 had been established as the principal NADase in mammalian tissues, with CD38 expression increasing with age and contributing to the age-associated decline in tissue NAD⁺ levels. The Escande et al. demonstration that apigenin increased NAD⁺ through CD38

inhibition, and that this increase activated sirtuin-dependent deacetylation pathways and improved metabolic parameters in obese mice, positioned apigenin within the rapidly expanding NAD⁺ biology and longevity research field.

3.4 Cancer pharmacology expansion

The anti-cancer pharmacology of apigenin expanded substantially from the 1990s onward. Gupta et al. (2001) published the initial demonstration that apigenin inhibited prostate cancer cell growth through induction of WAF1/p21 and INK4a/p16 cyclin-dependent kinase inhibitors and G1 cell cycle arrest [10]. Subsequent work across multiple cancer types established a broad anti-proliferative and pro-apoptotic profile involving PI3K/AKT, MAPK/ERK, NF-kappaB, Wnt/beta-catenin, and JAK/STAT signaling pathway modulation [11]. A 2022 systematic review and meta-analysis of 25 animal cancer studies confirmed significant tumor volume reduction across liver, prostate, pancreatic, lung, breast, and colon cancer models [14].

3.5 Current research-clinical status

Apigenin has not been developed as a registered pharmaceutical for any indication. No investigational new drug application for purified apigenin has been filed with the United States Food and Drug Administration or any other major regulatory authority. The compound is commercially available as a dietary supplement (not subject to pre-market efficacy review) and as a research chemical. The current research-clinical state is one of extensive and expanding preclinical pharmacology, limited human pharmacokinetic data, and essentially absent controlled clinical trial evidence for the isolated compound.

4. Mechanism of Action

Apigenin is a multi-target compound. Its principal molecular activities, characterized in cell-free, cellular, and animal systems, are inhibition of CD38 NADase activity; modulation of the GABA-A receptor at the benzodiazepine binding site; competitive inhibition of aromatase (CYP19A1); and suppression of NF-kappaB-mediated inflammatory transcription. Additional characterized activities include inhibition of protein kinases (casein kinase 2, cyclin-dependent kinases), modulation of the PI3K/AKT/mTOR and MAPK/ERK signaling cascades, direct antioxidant radical scavenging, and inhibition of xanthine oxidase. The breadth of the target profile reflects the planar polyphenolic structure, which permits binding across diverse protein active sites and allosteric pockets.

4.1 CD38 inhibition and NAD⁺ metabolism

CD38 is a type II transmembrane glycoprotein expressed on the surface of immune cells, hepatocytes, neurons, adipocytes, and other tissues. It functions as an ectoenzyme with NADase, ADP-ribosyl cyclase, and cyclic ADP-ribose hydrolase activities, consuming NAD⁺ to produce nicotinamide, ADP-ribose, and cyclic ADP-ribose [15]. CD38 is the dominant NAD⁺-degrading enzyme in mammalian tissues and is the principal determinant of the age-associated decline in tissue NAD⁺ levels, with CD38 expression increasing approximately two- to three-fold in aged mouse tissues compared to young tissues.

Apigenin inhibits CD38 enzymatic activity. The Escande et al. (2013) study demonstrated that apigenin treatment of wild-type mouse embryonic fibroblasts increased intracellular NAD⁺ levels, while treatment of CD38 knockout cells had no effect on NAD⁺, confirming that the NAD⁺ elevation is specifically mediated through CD38 inhibition [1]. In diet-induced obese C57BL/6 mice, oral apigenin administration increased liver and muscle NAD⁺ levels, decreased global protein acetylation (consistent with increased sirtuin deacetylase activity consequent to NAD⁺ elevation), decreased acetylation of the sirtuin substrates p53 and RelA-p65, and improved glucose tolerance, hepatic steatosis, and lipid profiles.

The downstream consequences of CD38 inhibition and NAD⁺ elevation include activation of the sirtuin family of NAD⁺-dependent protein deacetylases (SIRT1 through SIRT7), with SIRT1 (nuclear) and SIRT3 (mitochondrial) being the best-characterized mediators of the metabolic improvements. SIRT1 activation deacetylates and activates PGC-1 α (peroxisome proliferator-activated receptor gamma coactivator 1- α), promoting mitochondrial biogenesis and fatty acid oxidation. SIRT3 activation maintains mitochondrial protein homeostasis and reduces mitochondrial oxidative stress [16].

Jang et al. (2020) demonstrated that CD38 inhibition by apigenin ameliorated mitochondrial oxidative stress through restoration of the intracellular NAD⁺/NADH ratio and SIRT3 activity in renal tubular cells in a diabetic rat model, extending the metabolic applications of the CD38-NAD⁺-sirtuin mechanism to diabetic nephropathy [16].

4.2 GABA-A receptor modulation

The gamma-aminobutyric acid type A (GABA-A) receptor is a heteropentameric ligand-gated chloride channel of the Cys-loop superfamily, composed of combinations of α , β , γ , δ , ϵ , π , θ , and ρ subunits. The most prevalent synaptic assembly is α -1/ β -2/ γ -2. The benzodiazepine binding site is located at the interface between the α and γ subunits and is the target of the classical benzodiazepine anxiolytics (diazepam, lorazepam, alprazolam) and the Z-drugs (zolpidem, zaleplon).

Viola et al. (1995) demonstrated that apigenin displaced [3H]flumazenil from the benzodiazepine binding site in rat cerebellar membranes with an IC₅₀ of approximately 250 micromolar, indicating weak but measurable affinity [2]. In behavioral assays, apigenin at intraperitoneal doses of 1 to 3 mg/kg produced anxiolytic effects in the elevated plus maze (increased open-arm time) and in the open field (increased center exploration) without producing the sedation, amnesia, or myorelaxation characteristic of full benzodiazepine agonists at comparable anxiolytic doses. The Viola et al. report interpreted these findings as consistent with a partial agonist or anxioselective profile at the benzodiazepine site.

Subsequent studies have complicated this characterization. Avallone et al. (2000) reported that apigenin modulated GABAergic transmission in cultured cortical neurons and that the behavioral effects included both flumazenil-sensitive and flumazenil-insensitive components, suggesting that mechanisms beyond the ben-

zodiazepine binding site contribute to the in vivo activity [8]. Campbell et al. (2004) characterized apigenin electrophysiologically and found that it enhanced diazepam-mediated positive modulation of GABA-A receptor currents, a finding more consistent with a positive allosteric modulator than a direct benzodiazepine-site agonist [9]. The precise pharmacological classification of apigenin at the GABA-A receptor remains unresolved and likely depends on receptor subunit composition and local concentration.

The behavioral consequence relevant to human use is the anxiolytic and mildly sedative activity that underpins the traditional use of chamomile preparations for relaxation and sleep. The contribution of apigenin to the overall activity of chamomile extract is plausible but not definitively isolated from the contributions of other chamomile constituents (bisabolol, chamazulene, other flavonoids).

4.3 Aromatase (CYP19A1) inhibition

Aromatase (CYP19A1) is the cytochrome P450 enzyme that catalyzes the final step in estrogen biosynthesis: the aromatization of androstenedione to estrone and of testosterone to estradiol. Aromatase inhibition reduces circulating estrogen levels and is the principal pharmacological strategy in hormone-receptor-positive breast cancer (anastrozole, letrozole, exemestane).

Apigenin inhibits aromatase with an IC₅₀ of approximately 20 to 23 micromolar in H295R human adrenocortical carcinoma cells and in human placental microsomes [6]. Among the dietary flavones, chrysin is a more potent aromatase inhibitor (IC₅₀ approximately 1 to 2 micromolar), while apigenin is more potent than quercetin and kaempferol at this target. The aromatase inhibition is competitive with the androgen substrate, consistent with binding at or near the active-site heme.

The functional consequence at dietary doses is uncertain. At supplemental doses of 50 to 500 mg, the achievable plasma concentrations of free apigenin (given the approximately 30 percent oral bioavailability and the approximately 2.5-hour half-life) are likely below the IC₅₀ for aromatase inhibition. Pharmacologically meaningful aromatase inhibition in vivo would require sustained plasma concentrations in the low-micromolar range, which may be achievable only at higher supplemental doses or with formulation strategies that improve bioavailability.

The relationship between apigenin and estrogen signaling is dose-dependent and bidirectional. Long et al. (2008) demonstrated that low concentrations of apigenin (below 10 micromolar) enhanced estrogen receptor alpha (ERalpha) transcriptional activity, while higher concentrations inhibited ERalpha mobility, down-regulated ERalpha and co-activator expression, and inhibited multiple protein kinases [17]. This biphasic dose-response has implications for the interpretation of both preclinical and clinical studies.

4.4 Anti-inflammatory signaling

Apigenin suppresses NF-kappaB-driven inflammatory gene transcription through multiple converging mechanisms. Direct inhibition of IKK-beta (the kinase that phosphorylates the inhibitor of NF-kappaB, IkappaB-alpha, triggering its degradation and NF-kappaB nuclear translocation) has been characterized in macrophage cell lines [7]. Upstream, apigenin inhibits the lipopolysaccharide-induced activation of TLR4 signaling, reduces phosphorylation of p38 MAPK and JNK, and suppresses STAT3 activation. The aggregate consequence is reduced production of TNF-alpha, IL-1beta, IL-6, prostaglandin E2, nitric oxide, and other pro-inflammatory mediators.

In addition to the NF-kappaB pathway, apigenin suppresses cyclooxygenase-2 (COX-2) expression at the transcriptional level and inhibits inducible nitric oxide synthase (iNOS) expression. These activities are complementary to the direct radical-scavenging antioxidant activity of the flavone structure, producing a composite anti-inflammatory and antioxidant profile [18].

4.5 Additional molecular targets

Apigenin has documented activity against several additional molecular targets, including:

Casein kinase 2 (CK2): competitive inhibition at the ATP-binding site with K_i approximately 0.2 to 1 micromolar, one of the most potent characterized activities of apigenin [19]. CK2 is a constitutively active serine/threonine kinase involved in cell survival, proliferation, and inflammatory signaling. CK2 inhibition contributes to the pro-apoptotic activity in cancer cells.

Cyclin-dependent kinases (CDK1, CDK2, CDK4): apigenin induces cell cycle arrest at G0/G1 and G2/M through upregulation of CDK inhibitors (p21WAF1/CIP1, p27KIP1, p16INK4a) and through direct or indirect effects on CDK activity [10].

NMDA glutamate receptors: apigenin inhibits NMDA receptor-mediated currents and confers neuroprotection against glutamate excitotoxicity in cortical and hippocampal neuron cultures [12].

Acetylcholinesterase (AChE): moderate inhibition has been reported in some assays, contributing to the neuroprotective profile in Alzheimer's disease models, though potency is lower than that of approved AChE inhibitors [13].

Xanthine oxidase: inhibition at low-micromolar concentrations reduces uric acid production and reactive oxygen species generation from xanthine metabolism [18].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Apigenin is absorbed from the gastrointestinal tract after oral administration, though bioavailability is limited by poor aqueous solubility and extensive first-pass conjugation. Oral bioavailability in rats has been estimated at approximately 30 percent [20]. In a human pharmacokinetic study, Nielsen et al. (1999) administered parsley-enriched meals containing defined apigenin content and measured plasma apigenin concentrations; the compound was detectable in plasma at peak concentrations of approximately 100 to 200 nanomolar after meals providing approximately 3 to 4 mg of apigenin [21]. Chen et al. (2022) conducted a more formal pharmacokinetic assessment of apigenin and its glycosides in healthy male adults, reporting measurable plasma levels of apigenin glucuronide and sulfate conjugates [22].

Time to peak plasma concentration (T_{max}) after oral administration is approximately 0.5 to 2.5 hours, with variability depending on the formulation (aglycone versus glycoside), the food matrix, and individual intestinal metabolism.

5.2 Distribution

Apigenin distributes broadly to tissues. The compound crosses the blood-brain barrier, as confirmed by detection of apigenin in brain tissue after oral administration in rodents and by the observed central nervous system pharmacological effects (anxiolytic, neuroprotective) [12]. Plasma protein binding is high (approximately 92 to 95 percent), predominantly to albumin. Volume of distribution data in humans are not well characterized.

5.3 Metabolism

Apigenin undergoes extensive metabolism through both Phase I and Phase II pathways.

Phase I (oxidative) metabolism: The principal oxidative transformation is hydroxylation of the B-ring at the 3' position, producing luteolin (3',4',5,7-tetrahydroxyflavone) as the major Phase I metabolite. Additional minor hydroxylated products include scutellarein (5,6,7,4'-tetrahydroxyflavone) and isoscutellarein (5,7,8,4'-tetrahydroxyflavone). The cytochrome P450 isoforms responsible include CYP1A1, CYP1A2, CYP1B1, CYP2B, and CYP2E1 [20].

Phase II (conjugation) metabolism: Apigenin is extensively conjugated by UDP-glucuronosyltransferases (UGTs) and sulfotransferases (SULTs), producing glucuronide and sulfate conjugates at the 7-OH and 4'-OH positions. Three monoglucuronconjugates and one monosulfoconjugate have been identified. The circulating forms in plasma are predominantly the glucuronide and sulfate conjugates rather than the free aglycone [22].

5.4 Elimination

The plasma elimination half-life of apigenin after oral administration is approximately 2 to 3 hours in the limited human pharmacokinetic data available. Elimination is predominantly through biliary and urinary excretion of the conjugated metabolites. Enterohepatic recirculation of glucuronide conjugates has been demonstrated in animal models and may contribute to a secondary plasma peak in some subjects.

Intestinal microbiota contribute to the metabolism of apigenin glycosides by hydrolyzing the sugar moieties to release the aglycone for absorption or further bacterial metabolism to ring-fission products (phloretin-type metabolites and phenylpropionic acid derivatives) [22].

5.5 Routes of administration

Oral administration is the standard route for both dietary consumption and supplemental use. The aglycone is available in capsule and tablet formulations at doses of 50 to 500 mg. Research applications use apigenin dissolved in dimethyl sulfoxide (DMSO) for in vitro work (stock solutions at 10 to 100 millimolar) and in corn oil, olive oil, or carboxymethylcellulose suspensions for oral gavage in animal studies. Intraperitoneal injection in rodent studies typically uses DMSO-saline or DMSO-corn oil vehicles.

5.6 Drug-drug interaction potential

Apigenin inhibits CYP2C9 in vitro and may affect the metabolism of CYP2C9 substrates including warfarin, phenytoin, and several nonsteroidal anti-inflammatory drugs [23]. Apigenin also inhibits CYP3A4 and P-glycoprotein; Li et al. (2013) demonstrated that apigenin pretreatment increased the oral bioavailability of imatinib and its active metabolite N-desmethyl imatinib in rats through inhibition of CYP3A4 and P-glycoprotein-mediated efflux [24]. The clinical relevance of these interactions at dietary doses (less than 5 mg daily) is likely negligible, but at supplemental doses (50 to 500 mg daily) the interaction potential is uncertain and has not been evaluated in human drug-interaction studies.

6. Preclinical Pharmacology

6.1 Anti-cancer activity

The preclinical anti-cancer pharmacology of apigenin is extensive and spans multiple tumor types and mechanistic pathways.

Prostate cancer: Gupta et al. (2001, 2002) demonstrated that oral apigenin administration (20 and 50 micrograms per mouse per day for 20 weeks) to TRAMP (transgenic adenocarcinoma of mouse prostate) mice reduced tumor volumes in a dose-dependent manner, with complete abolishment of distant organ metastasis at the 50-microgram dose [10]. The mechanism involved upregulation of WAF1/p21, KIP1/p27, INK4a/p16, and INK4c/p18 cyclin-dependent kinase inhibitors and down-regulation of cyclins D1, D2, and E, producing G0/G1 cell cycle arrest and apoptosis.

Breast cancer: Long et al. (2008) demonstrated that apigenin inhibited antiestrogen-resistant breast cancer cell growth through both ERalpha-dependent and ERalpha-independent mechanisms, including inhibition of PI3K/AKT and MAPK/ERK signaling [17]. In vivo studies using MDA-MB-231 xenograft models have demonstrated tumor growth inhibition at oral doses of 25 to 50 mg/kg.

Pancreatic cancer: Johnson et al. (2009) reported enhanced anti-tumor effects of the combination of apigenin with gemcitabine in pancreatic cancer cell lines and in orthotopic xenograft models, with apigenin sensitizing gemcitabine-resistant cells through suppression of NF-kappaB and GSK-3beta/NF-kappaB signaling [25].

Meta-analysis: Xu et al. (2022) conducted a systematic review and meta-analysis of 25 in vivo animal cancer studies and found a significant overall reduction in tumor volume (standardized mean difference = -3.597, 95% CI: -4.502 to -2.691, $p < 0.001$) across liver, prostate, pancreatic, lung, breast, and colon cancer models [14].

6.2 Neuroprotection

Apigenin crosses the blood-brain barrier and produces neuroprotective effects in multiple disease models.

Alzheimer's disease: In APP/PS1 transgenic mice, apigenin reduced amyloid-beta plaque deposition, attenuated tau hyperphosphorylation, and improved spatial memory in the Morris water maze [12]. The neuroprotective mechanisms include suppression of microglial NF-kappaB activation and inflammatory cytokine production (TNF-alpha, IL-1beta, IL-6), reduction of oxidative stress through upregulation of endogenous antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase), and promotion of synaptogenesis through activation of the ERK/CREB/BDNF signaling pathway [13].

Parkinson's disease: In MPTP-treated mice and 6-OHDA-lesioned rat models, apigenin improved motor function (reduced pole test scores, improved rotarod performance, improved grip strength) and protected dopaminergic neurons in the substantia nigra through anti-inflammatory and antioxidant mechanisms [13].

Excitotoxicity: Apigenin inhibits NMDA receptor-mediated excitotoxicity in cultured cortical and hippocampal neurons, reducing calcium influx and subsequent calpain activation and mitochondrial membrane depolarization [12].

Systematic review: Yusuf et al. (2024) conducted a systematic review of preclinical investigations of apigenin in cognitive and neurobehavioral dysfunction, finding consistent evidence for enhanced learning and memory, improved locomotion, anxiolytic effects, attenuated depressive-like behavior, and improved sensorimotor coordination across multiple disease models [26].

6.3 Metabolic endpoints

The CD38-NAD⁺-sirtuin axis is the principal molecular mechanism underpinning the metabolic preclinical pharmacology.

Obesity and insulin resistance: Escande et al. (2013) demonstrated improvements in glucose tolerance, insulin sensitivity, and hepatic steatosis in diet-induced obese mice treated with apigenin, with the metabolic improvements correlating with elevated tissue NAD⁺ levels and reduced protein acetylation [1].

Diabetic nephropathy: Jang et al. (2020) demonstrated that apigenin ameliorated mitochondrial oxidative stress in diabetic rat renal tubular cells through CD38 inhibition, restoration of the NAD⁺/NADH ratio, and consequent SIRT3 reactivation [16].

Cardiovascular protection: Preclinical studies have demonstrated cardioprotective effects through attenuation of ischemia-reperfusion injury, reduction of atherosclerotic plaque formation through anti-inflammatory mechanisms, and improvement of endothelial function through enhanced nitric oxide bioavailability [18].

6.4 Anti-inflammatory activity

Beyond the NF-kappaB suppression described in the mechanism of action section, apigenin demonstrates anti-inflammatory activity in multiple in vivo models. In lipopolysaccharide-challenged mice, apigenin reduces circulating TNF-alpha, IL-1beta, and IL-6 levels. In carrageenan-induced paw edema models, apigenin reduces edema at oral doses of 25 to 50 mg/kg. In colitis models (DSS-induced and TNBS-induced), apigenin attenuates mucosal inflammation and reduces disease activity scores [7, 18].

7. Clinical Evidence Base

7.1 Chamomile extract studies (apigenin as constituent)

The majority of human clinical evidence relevant to apigenin derives from studies of chamomile (*Matricaria recutita*) extract, in which apigenin is present as one of several biologically active constituents.

Anxiety: Amsterdam et al. (2009) conducted a randomized, double-blind, placebo-controlled trial of chamomile extract standardized to 1.2 percent apigenin in 57 patients with mild to moderate generalized anxiety disorder [27]. Eight weeks of chamomile extract (220 mg capsules, one to five daily) produced a significant reduction in Hamilton Anxiety Rating Scale scores compared to placebo. A subsequent long-term study by the same group (Amsterdam et al. 2012) confirmed tolerability and suggested sustained anxiolytic benefit over 8 weeks [28]. Mao et al. (2016) conducted a 38-week randomized placebo-controlled trial in 179 patients with moderate to severe generalized anxiety disorder, demonstrating that chamomile extract (1500 mg daily, standardized to apigenin content) significantly reduced mean GAD-7 scores compared to placebo during the active treatment phase [29].

Sleep: Zick et al. (2011) reported a randomized controlled trial of chamomile extract in 34 patients with primary insomnia, with modest improvements in sleep diary measures but no significant difference in the primary endpoint (Pittsburgh Sleep Quality Index) compared to placebo [30].

Limitations: These studies employed chamomile extract rather than purified apigenin. The contribution of apigenin to the observed effects cannot be definitively separated from the contributions of bisabolol, chamazulene, luteolin, and other chamomile constituents. The apigenin content of the chamomile extracts ranged from 1.2 to 3.5 percent, providing approximately 3 to 50 mg of apigenin per day depending on the study and dose level.

7.2 Isolated apigenin studies

Pharmacokinetics: Nielsen et al. (1999) administered parsley-enriched meals to healthy volunteers and measured plasma apigenin kinetics, establishing the time course of absorption and conjugation for dietary apigenin [21]. Chen et al. (2022) characterized the absorption, distribution, metabolism, and excretion of apigenin and its glycosides in healthy male adults, identifying the major circulating metabolites as glucuronide and sulfate conjugates [22].

Dietary association studies: Epidemiological analyses of dietary flavonoid intake have associated higher apigenin consumption with reduced risk of certain cancers and cardiovascular events, though these observational data are subject to confounding by overall dietary quality and other flavonoid co-consumption [3].

Supplement studies: Controlled clinical trials of purified apigenin supplementation for specific health endpoints have not been published in peer-reviewed literature as of the most recent monograph revision. The compound is available as a dietary supplement; supplement-dose human efficacy data are absent.

7.3 Ongoing and planned research

The current research trajectory for apigenin is principally preclinical, with the most active areas being NAD⁺ restoration and aging biology, neuroprotection and neurodegeneration, cancer chemoprevention, and metabolic syndrome. Translation to controlled human clinical trials with purified apigenin at defined doses for specific endpoints remains an unmet milestone.

8. Sourcing and Quality Verification

Apigenin is commercially available from multiple sources as both a dietary supplement and a research-grade chemical.

Dietary supplement grade: Numerous supplement manufacturers supply apigenin capsules at 50 mg, 100 mg, 250 mg, or 500 mg per unit. Supplement-grade material is typically extracted from chamomile flowers or celery seeds and is standardized to 95 to 98 percent purity by HPLC. Supplement products are not subject to pre-market purity verification by regulatory authorities, and independent testing of supplement products has occasionally identified purity below the label claim.

Research grade: Sigma-Aldrich (MilliporeSigma), Cayman Chemical, Santa Cruz Biotechnology, Tocris, MedChemExpress, and BOC Sciences supply apigenin at greater than 95 to 99 percent purity by HPLC, in milligram to gram quantities. Research-grade pricing is moderate, in the range of \$20 to \$100 per gram at greater than 98 percent purity at the time of monograph preparation.

Verification: Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography area-percent purity, ideally greater than 98 percent
- Mass spectrometry confirmation of molecular weight (271.06 for the protonated molecular ion $[M+H]^+$)
- Ultraviolet-visible spectrophotometry (characteristic absorption maxima at approximately 267 nm and 336 nm in methanol)
- Melting point determination (345 to 350 degrees Celsius with decomposition)
- Residual solvent analysis by gas chromatography if the material was purified using organic solvents

Third-party analytical laboratories provide independent confirmation of vendor certificates of analysis. The apigenin supply chain is well established; the principal quality concern is purity in supplement-grade products rather than identity.

9. Reconstitution and Handling

Apigenin is poorly soluble in water (approximately 2.16 micrograms per milliliter at 25 degrees Celsius) and requires organic solvents or formulation strategies for most research applications.

In vitro stock solutions: Dissolve in dimethyl sulfoxide (DMSO) at 10 to 100 millimolar stock concentration. DMSO stock solutions should be aliquoted and stored at -20 degrees Celsius, protected from light. Stable for at least 6 months at -20 degrees Celsius in sealed aliquots. Final DMSO concentration in cell culture assays should not exceed 0.1 to 0.5 percent v/v to avoid solvent-mediated cytotoxicity.

In vivo formulations (oral gavage): Suspend in corn oil, olive oil, or 0.5 percent carboxymethylcellulose in water for oral gavage. Prepare fresh or use within 24 hours. For improved bioavailability, nanoparticle encapsulation (PLGA, liposomal, cyclodextrin inclusion complexes) has been demonstrated in preclinical studies.

In vivo formulations (intraperitoneal): Dissolve in DMSO and dilute to final concentration in sterile saline or phosphate-buffered saline. DMSO content in the injection vehicle should not exceed 10 percent v/v.

Storage: Solid material should be stored at -20 degrees Celsius, desiccated, and protected from light. The compound is stable for at least 2 years under these conditions. At room temperature in dry conditions, stability is adequate for short-term handling (weeks) but long-term storage at room temperature is not recommended for research applications.

Light sensitivity: Apigenin is moderately photosensitive. Amber vials or aluminum foil wrapping is recommended for solution storage.

10. Stack Interactions and Combinations

Apigenin interacts with several compound classes through its multi-target pharmacology and its CYP inhibitory profile. Investigators conducting research with apigenin in combination regimens should consider:

NAD⁺ precursors (nicotinamide mononucleotide, nicotinamide riboside): The combination of CD38 inhibition (apigenin) with NAD⁺ precursor supplementation is mechanistically rational and has been proposed in the longevity research community as a strategy for maximizing NAD⁺ elevation through simultaneous enhancement of synthesis and reduction of degradation. No published study has evaluated this combination in a controlled setting, and the combination pharmacokinetics and pharmacodynamics have not been characterized.

Benzodiazepines and Z-drugs: Concurrent administration with benzodiazepine-site ligands (diazepam, zolpidem) may produce additive or competitive effects at the GABA-A receptor, depending on the precise nature of the apigenin-receptor interaction at the relevant concentration. The clinical relevance is uncertain at dietary doses but plausible at supplemental doses of 250 to 500 mg. Additive sedation should be anticipated.

Aromatase inhibitors (anastrozole, letrozole, exemestane): Apigenin's moderate aromatase inhibition may produce additive estrogen suppression with pharmaceutical aromatase inhibitors. The magnitude of the interaction at supplemental doses is likely small given the much higher potency of pharmaceutical aromatase inhibitors.

CYP2C9 substrates (warfarin, phenytoin, celecoxib): Apigenin inhibition of CYP2C9 may increase exposure to CYP2C9 substrates. The clinical relevance has not been evaluated in human drug-interaction studies. Investigators using apigenin concurrently with narrow-therapeutic-index CYP2C9 substrates should monitor for signs of increased substrate exposure.

CYP3A4 substrates: Apigenin inhibition of CYP3A4 may increase exposure to CYP3A4 substrates, including many statins, calcium channel blockers, immunosuppressants, and protease inhibitors [24]. Li et al. (2013) demonstrated increased imatinib bioavailability in rats after apigenin pretreatment.

Quercetin and other flavonoids: Concurrent administration of multiple dietary flavonoids is common in supplement regimens and in high-flavonoid diets. Additive or synergistic effects on shared targets (NF-kappaB, COX-2, antioxidant enzymes) are plausible. Competition for the same Phase II conjugation pathways (UGT, SULT) may alter the pharmacokinetics of co-administered flavonoids.

Chemotherapy agents: Preclinical evidence supports combination of apigenin with gemcitabine (pancreatic cancer), 5-fluorouracil (colon cancer), and cisplatin (various solid tumors) for additive or synergistic anti-tumor effects [25]. Translation to human combination therapy has not been attempted.

11. Adverse Events and Safety

11.1 Preclinical toxicology

Apigenin is non-mutagenic and non-genotoxic in standard regulatory toxicology assays (Ames test, micronucleus assay, chromosomal aberration assay). Acute oral toxicity studies in mice have established a no-observed-adverse-effect level at approximately 50 mg/kg. Intraperitoneal administration at 100 to 200 mg/kg has produced hepatotoxicity (elevated liver transaminases, hepatocellular necrosis) in mice, indicating a clear dose-dependent toxicity threshold [14]. Chronic oral toxicity studies in rats at doses up to 100 mg/kg/day for 13 weeks have not produced significant organ toxicity or hematologic abnormalities.

Reproductive toxicity data are limited. The aromatase inhibitory activity raises a theoretical concern for estrogen-dependent developmental processes at high doses, but no teratogenicity has been reported in published animal studies.

11.2 Human safety data

Human safety data for purified apigenin at supplemental doses are limited. Chamomile extract studies (which provide approximately 3 to 50 mg of apigenin daily depending on the preparation) have reported a safety profile comparable to placebo, with no serious adverse events in trials extending to 38 weeks [27, 28, 29].

Supplement use at doses of 50 to 500 mg daily has been reported in consumer and clinical anecdotal experience. The most commonly reported adverse effects are:

- Drowsiness and sedation (consistent with GABA-A receptor activity; principally at doses of 250 mg and above or at bedtime)
- Mild gastrointestinal discomfort (nausea, bloating; infrequent)

No serious adverse events have been reported in the published literature or in post-marketing surveillance databases for apigenin as a dietary supplement.

11.3 Drug interaction concerns

The CYP2C9, CYP3A4, and P-glycoprotein inhibitory activities raise theoretical drug interaction concerns, particularly for individuals taking warfarin, phenytoin, certain statins, or immunosuppressants concurrently with high-dose apigenin supplementation. No clinical drug interaction studies with purified apigenin have been published.

11.4 Pregnancy and lactation

Safety in pregnancy and lactation has not been established for apigenin supplementation. The aromatase inhibitory and estrogen-modulating activities suggest caution in pregnancy. Chamomile tea consumption during pregnancy has not been associated with adverse outcomes in epidemiological studies, but the apigenin doses from tea consumption are substantially lower than from supplementation.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five structurally or functionally related flavonoid compounds against apigenin, evaluated against five competency standards: novelty (uniqueness of the pharmacological profile), effect size (magnitude of demonstrated biological activity), promising potential (current trajectory and translational prospects), side-effect profile (clinical or preclinical safety), and overall validation (depth and quality of the evidence base). The five comparators were selected to span the structural relatives within the flavone and flavonol subclasses and to include compounds that share one or more of apigenin's principal molecular targets.

12.1 Luteolin (3',4',5,7-tetrahydroxyflavone)

Structural relationship: Luteolin differs from apigenin by a single hydroxyl group at the 3' position of the B-ring. It is the immediate oxidative metabolite of apigenin in mammalian Phase I metabolism and is also a dietary flavonoid in its own right (abundant in celery, green pepper, perilla, chamomile).

Pharmacological profile: Luteolin shares the anti-inflammatory (NF-kappaB suppression), antioxidant, anti-cancer (cell cycle arrest, apoptosis induction), and neuroprotective activities of apigenin [31]. The additional catechol (3',4'-dihydroxy) B-ring motif confers greater antioxidant radical-scavenging activity (lower DPPH and ORAC values) and greater metal-chelation capacity. Luteolin is a more potent inhibitor of xanthine oxidase than apigenin. Both compounds inhibit CK2 with comparable potency.

Novelty: Low. The pharmacological profile substantially overlaps with apigenin; the additional hydroxyl group enhances some activities but does not introduce novel target engagement.

Effect size: Comparable to apigenin in most assays; modestly greater antioxidant and anti-inflammatory activity in head-to-head in vitro comparisons.

Promising potential: Moderate. Similar preclinical trajectory to apigenin. No clinical trials with purified luteolin have been completed.

Side-effect profile: Comparable to apigenin. The catechol motif introduces theoretical pro-oxidant activity at high concentrations through redox cycling, though this has not been a practical concern in preclinical studies.

Overall validation: Moderate. Extensive preclinical literature; no clinical evidence with purified compound.

Comparison to apigenin: Luteolin is a close structural and pharmacological relative with incrementally greater antioxidant potency. Apigenin has the advantage of the characterized CD38 inhibitory activity (which has not been formally studied for luteolin at comparable rigor) and the broader supplement market presence. The two compounds are complementary research tools.

12.2 Chrysin (5,7-dihydroxyflavone)

Structural relationship: Chrysin lacks the 4'-hydroxyl group on the B-ring that is present in apigenin. It is the simplest dihydroxyflavone and is found in honey, propolis, and passionflower.

Pharmacological profile: Chrysin is a more potent aromatase inhibitor than apigenin (IC₅₀ approximately 1 to 2 micromolar versus 20 to 23 micromolar for apigenin) and has been marketed in supplement formulations as a "natural aromatase inhibitor" [6]. Chrysin shares the anti-inflammatory and antioxidant activities of the flavone class but has lower potency than apigenin and luteolin at most anti-inflammatory endpoints, reflecting the reduced hydroxylation pattern. Chrysin has been reported to bind the GABA-A receptor at the benzodiazepine site with similar or slightly greater affinity than apigenin in some radioligand displacement assays [32].

Novelty: Low. The pharmacological profile is a subset of the apigenin profile, with the exception of the stronger aromatase inhibition.

Effect size: Stronger aromatase inhibition in vitro; weaker anti-inflammatory and antioxidant activity. Oral bioavailability is extremely low (less than 5 percent in most estimates), severely limiting in vivo effect sizes at practical doses.

Promising potential: Low. The extremely poor bioavailability has been a consistent limitation. No clinical trial evidence exists for any endpoint.

Side-effect profile: Limited safety data. No serious adverse events reported in preclinical studies.

Overall validation: Low. The compound is commercially popular as a supplement but has weak scientific validation at supplemental doses due to the bioavailability limitation.

Comparison to apigenin: Chrysin has superior in vitro aromatase inhibition but substantially inferior oral bioavailability and a narrower pharmacological profile. Apigenin is the more pharmacologically versatile and biologically accessible compound.

12.3 Quercetin (3,3',4',5,7-pentahydroxyflavone)

Structural relationship: Quercetin is a flavonol (3-hydroxyflavone) rather than a flavone, differing from apigenin by hydroxyl groups at the 3 and 3' positions. It is the most abundant dietary flavonoid, present in onions, apples, berries, and many vegetables.

Pharmacological profile: Quercetin has a broader and more extensively studied pharmacological profile than apigenin, with characterized activities including potent antioxidant radical scavenging (the most potent common dietary flavonoid in DPPH and ORAC assays), NF-kappaB suppression, anti-cancer activity across multiple tumor types, cardioprotective effects, and senolytic activity (selective clearing of senescent cells in combination with dasatinib, the Kirkland laboratory "D+Q" protocol) [33]. Quercetin is a weaker aromatase inhibitor than apigenin or chrysin. Quercetin does not have the characterized CD38 inhibitory activity that distinguishes apigenin.

Novelty: Moderate. The senolytic activity (Zhu et al. 2015, in combination with dasatinib) represents a novel pharmacological application not shared by apigenin [33].

Effect size: Greater antioxidant potency than apigenin; comparable anti-inflammatory potency; demonstrated senolytic activity at achievable concentrations. Oral bioavailability is low (approximately 1 to 5 percent for the aglycone) but can be improved with lipid formulations.

Promising potential: Moderate to high. The senolytic combination with dasatinib has advanced to human pilot studies. Multiple clinical trials with quercetin supplementation for cardiovascular and metabolic endpoints have been completed with modest positive results.

Side-effect profile: Generally safe at supplemental doses. Inhibition of CYP3A4 and CYP2C9 raises drug-interaction concerns similar to apigenin.

Overall validation: Moderate to high. The most extensively studied dietary flavonoid; more human clinical trial data than apigenin; the senolytic application has generated substantial translational interest.

Comparison to apigenin: Quercetin has a larger research literature, more clinical evidence, and the unique senolytic application. Apigenin has the unique CD38 inhibitory and GABA-A modulatory activities. The two compounds are mechanistically complementary and are frequently co-administered in supplement regimens.

12.4 Kaempferol (3,4',5,7-tetrahydroxyflavone)

Structural relationship: Kaempferol is a flavonol differing from apigenin by a hydroxyl group at the 3 position. It is the 3-hydroxy derivative of apigenin. Found in tea, broccoli, kale, berries, and other dietary sources.

Pharmacological profile: Kaempferol shares the anti-inflammatory, antioxidant, and anti-cancer activities of the flavone/flavonol class [34]. It has been reported to inhibit angiogenesis through VEGF receptor signaling suppression, to modulate estrogen receptor activity, and to produce neuroprotective effects in Alzheimer's disease models through inhibition of beta-secretase (BACE1) activity.

Novelty: Low. The pharmacological profile overlaps substantially with apigenin and quercetin.

Effect size: Comparable to apigenin in most anti-inflammatory and antioxidant assays; weaker antioxidant than quercetin (fewer hydroxyl groups); the BACE1 inhibitory activity is distinctive but of modest potency.

Promising potential: Low to moderate. Limited clinical evidence; no human trials with purified kaempferol for specific endpoints.

Side-effect profile: Generally safe at dietary doses. Preclinical toxicology data are limited.

Overall validation: Low to moderate. Substantial in vitro and in vivo preclinical data; essentially no clinical evidence.

Comparison to apigenin: Kaempferol has a comparable breadth of preclinical activity but lacks the CD38 inhibitory and GABA-A modulatory activities that distinguish apigenin. Apigenin has greater supplement market presence and more extensive pharmacological characterization at the single-target level.

12.5 Baicalein (5,6,7-trihydroxyflavone)

Structural relationship: Baicalein is a flavone with the same number of hydroxyl groups as apigenin but at different positions (5,6,7 rather than 4',5,7). It is the aglycone of baicalin and is the principal flavone of *Scutellaria baicalensis* (Chinese skullcap), a plant used extensively in traditional Chinese medicine.

Pharmacological profile: Baicalein has a distinct pharmacological profile from apigenin despite the shared flavone scaffold. It is a potent inhibitor of 12- and 15-lipoxygenase (12-LOX, 15-LOX), with IC₅₀ values in the low-micromolar range, distinguishing it from apigenin which has minimal lipoxygenase activity [35]. Baicalein has characterized anti-inflammatory, neuroprotective (including iron chelation and ferroptosis inhibition), anxiolytic (GABA-A modulation), and anti-viral activities.

Novelty: Moderate. The lipoxygenase inhibitory activity and the ferroptosis inhibition represent pharmacological activities not shared by apigenin.

Effect size: Potent lipoxygenase inhibition (IC₅₀ approximately 0.1 to 1 micromolar for 12-LOX); comparable anti-inflammatory potency to apigenin through NF-kappaB suppression.

Promising potential: Moderate. Clinical use in traditional Chinese medicine provides a long historical safety record. Limited controlled clinical trial evidence by Western regulatory standards; some clinical studies in China for inflammatory conditions.

Side-effect profile: Generally safe; long traditional use record. Potential for drug interactions through CYP inhibition similar to other flavonoids.

Overall validation: Moderate. Extensive preclinical data; limited Western clinical evidence; substantial traditional medicine evidence base.

Comparison to apigenin: Baicalein and apigenin have complementary pharmacological profiles despite the shared flavone scaffold. Baicalein has the unique lipoxygenase and ferroptosis targets; apigenin has the unique CD38 and GABA-A targets. The two compounds represent interesting comparators for structure-activity relationship analysis of the B-ring versus A-ring hydroxylation pattern in determining target selectivity.

12.6 Comparator summary

The five compounds occupy distinct positions in the flavonoid pharmacology space. **Luteolin** is the closest structural and pharmacological relative, differing by a single hydroxyl group and offering incrementally greater antioxidant potency. **Chrysin** has the strongest in vitro aromatase inhibition but is severely limited by poor bioavailability. **Quercetin** has the broadest research literature and the unique senolytic application but lacks apigenin's CD38 and GABA-A activities. **Kaempferol** has a comparable breadth of activity without the differentiating features that give apigenin its current research positioning. **Baicalein** has a complementary profile centered on lipoxygenase inhibition and ferroptosis prevention rather than CD38 and GABA-A modulation.

Apigenin occupies a distinctive position in this landscape through the convergence of CD38 NADase inhibition (positioning it within the NAD⁺ restoration and longevity research framework), GABA-A receptor modulation (positioning it within the anxiolytic and sleep research space), moderate aromatase inhibition (positioning it within the hormonal modulation space), and the broad anti-inflammatory and anti-cancer preclinical pharmacology shared with the flavonoid class generally. The compound is the most mechanistically differentiated of the dietary flavones for the specific combination of NAD⁺ biology and neuropsychiatric pharmacology. The principal limitation relative to quercetin is the smaller clinical evidence base; the principal advantage is the CD38 mechanism, which addresses an aspect of age-related metabolic decline (NAD⁺ degradation) not targeted by any of the comparator flavonoids.

Investigators considering apigenin for research applications should select the compound when the CD38-NAD⁺ mechanism, the GABA-A receptor activity, or the specific aromatase inhibitory profile is relevant to the research question. For general anti-inflammatory or antioxidant research, quercetin or luteolin may be

equally or more appropriate choices. For lipoxygenase-related research, baicalein is the superior candidate. For aromatase inhibition research where bioavailability is not a concern (in vitro work), chrysin offers greater potency.

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