

RESEARCH MONOGRAPH . COMPOUND PROFILE

Fisetin

A naturally occurring 3,7,3',4'-tetrahydroxyflavone identified as one of the most potent flavonoid senolytics, with convergent activity across PI3K/Akt/mTOR inhibition, SIRT1 activation, NF-kappaB suppression, and Nrf2-mediated antioxidant defense, positioned at the intersection of aging biology, neurodegeneration, and cancer chemoprevention research.

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ABSTRACT

Fisetin (3,7,3',4'-tetrahydroxyflavone) is a bioactive flavonol found at highest dietary concentration in strawberries and at lower levels in apples, persimmons, grapes, onions, and cucumbers. First isolated from the heartwood of Venetian sumac (*Cotinus coggygia*) in the late nineteenth century and characterized as a plant pigment, fisetin remained a minor flavonoid of limited pharmacological interest until convergent twenty-first-century discoveries established it as a multi-target agent active across the principal molecular pathways of cellular senescence, neurodegeneration, inflammation, and oncogenesis. The compound was identified as a potent senolytic in the landmark Zhu et al. (2017) screen at the Mayo Clinic Robert and Arlene Kogod Center on Aging, and the subsequent Yousefzadeh et al. (2018) demonstration that late-life oral fisetin administration extended median and maximum lifespan in wild-type mice while reducing senescence-associated markers in multiple tissues positioned it as the leading dietary flavonoid candidate for translational senolytic therapy [1, 2]. Mechanistically, fisetin operates through a convergent multi-pathway pharmacology: it inhibits PI3K/Akt/mTOR signaling by direct suppression of PI3K catalytic and regulatory subunit expression and by activation of the mTOR repressor TSC2 through concurrent AMPK phosphorylation; it activates SIRT1-dependent deacetylation cascades that suppress NF-kappaB transcriptional activity and the senescence-associated secretory phenotype (SASP); it induces Nrf2 nuclear translocation and downstream phase II antioxidant enzyme expression; and it modulates the Bcl-2 family balance toward pro-apoptotic signaling selectively in senescent cells [3, 4,

5]. The neuroprotective profile has been extensively characterized by the Maher laboratory at the Salk Institute for Biological Studies, where fisetin and its optimized derivative CMS121 have demonstrated efficacy in transgenic Alzheimer's disease mouse models through reduction of lipid peroxidation via fatty acid synthase (FASN) inhibition, suppression of neuroinflammatory cascades, and maintenance of glutathione homeostasis [6, 7]. CMS121 completed a Phase 1 clinical trial in 2025, with single doses up to 1800 mg and repeat doses up to 900 mg per day for 7 days demonstrating acceptable tolerability and favorable pharmacokinetic parameters in healthy volunteers [8]. The anticancer pharmacology spans preclinical efficacy in prostate, breast, colorectal, lung, melanoma, pancreatic, and bladder cancer models, principally through cell cycle arrest at G2/M and G1/S checkpoints, mitochondrial apoptosis induction, and suppression of epithelial-mesenchymal transition and matrix metalloproteinase expression [9, 10]. Clinical translation is constrained by the poor oral bioavailability characteristic of hydroxylated flavonols: fisetin undergoes rapid and extensive phase II conjugation (glucuronidation and sulfation) in the intestinal epithelium and liver, producing low systemic free flavonol concentrations after oral dosing; multiple formulation strategies (nanocochleates, liposomes, nanoemulsions, hybrid hydrogels) have demonstrated 10- to 140-fold bioavailability enhancement in preclinical and early human pharmacokinetic studies [11, 12]. Clinical trials led by the Kirkland laboratory at Mayo Clinic are evaluating fisetin at oral doses of 20 mg/kg per day for senolytic indications including frailty in aging (AFFINITY trial, NCT03675724), COVID-19 in skilled nursing facilities, and sepsis in elderly patients (STOP-Sepsis, NCT05758246) [13, 14]. This monograph reviews the chemistry, natural sourcing, and

structural pharmacology of fisetin; the multi-pathway molecular mechanism across senescence, inflammation, neuroprotection, and oncogenesis; the pharmacokinetic limitations and formulation solutions; the preclinical evidence base across aging, neurodegeneration, and cancer; the clinical trial landscape; sourcing and quality verification for research applications; reconstitution and handling; stack interactions; adverse-event signal; and a comparative assessment of five senolytic or flavonoid candidates against fisetin on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Common name: Fisetin.

Systematic (IUPAC) name: 2-(3,4-dihydroxyphenyl)-3,7-dihydroxychromen-4-one. The compound is a 3-hydroxyflavone (flavonol) bearing hydroxyl substituents at the 3, 7, 3', and 4' positions of the flavone nucleus.

Chemical Abstracts Service registry number: 528-48-3.

Other synonyms: 3,3',4',7-tetrahydroxyflavone; 5-deoxyquercetin; Fustel; Natural Brown 1 (CI 75620); 2-(3,4-dihydroxyphenyl)-3,7-dihydroxy-4H-chromen-4-one. The designation "5-deoxyquercetin" reflects the structural relationship to quercetin, from which fisetin differs only by the absence of the 5-hydroxyl group on the A-ring [15].

PubChem CID: 5281614.

ChEBI ID: CHEBI:42159.

DrugBank ID: DB07795.

UNII (FDA Substance Registration): OO2ABO9578.

1.2 Structural class and chemistry

Fisetin belongs to the flavonol subclass of flavonoids, a large family of plant polyphenolic secondary metabolites characterized by a 2-phenylchromen-4-one (flavone) backbone with a hydroxyl group at the 3-position. The flavonol class includes quercetin, kaempferol, myricetin, and isorhamnetin; fisetin is distinguished by its 3,7,3',4'-tetrahydroxylation pattern and the absence of the 5-hydroxyl that is present in most other dietary flavonols [15, 16].

Molecular formula: C₁₅H₁₀O₆.

Molecular weight: 286.24 g/mol (monoisotopic exact mass 286.0477 g/mol).

Physical properties: Yellow crystalline powder. Melting point 330 degrees Celsius (with decomposition). Poorly soluble in water (approximately 10.45 micrograms per milliliter at 25 degrees Celsius); soluble in dimethyl sulfoxide (DMSO), ethanol, methanol, and acetone. The compound exhibits characteristic flavonol ultraviolet absorption maxima at approximately 320 nm and 360 nm in methanolic solution.

Stereochemistry: Fisetin is achiral; the molecule contains no stereocenters and is supplied as a single constitutional isomer. The catechol (ortho-dihydroxyphenyl) moiety on the B-ring is the principal determinant of both the antioxidant radical-scavenging activity and the susceptibility to oxidative degradation and catechol-O-methyltransferase (COMT) methylation *in vivo*.

Key structure-activity relationships: The 3-hydroxyl group and the 2,3-double bond in conjugation with the 4-carbonyl (the defining features of the flavonol class) are required for the planarity that supports intercalation into enzyme active sites and for the electron delocalization that underpins radical scavenging. The catechol B-ring is required for high antioxidant potency and is the principal site of phase II metabolic conjugation. The absence of the 5-hydroxyl (present in quercetin) reduces intramolecular hydrogen bonding to the 4-carbonyl and modestly alters the redox potential and the protein-binding profile relative to quercetin [15].

1.3 Natural sources

Fisetin is present in a range of edible fruits and vegetables. The highest reported dietary concentrations are in strawberries (approximately 160 micrograms per gram wet weight), with lower concentrations in apples (approximately 26 micrograms per gram), persimmons (approximately 10 micrograms per gram), lotus root, onions, grapes, kiwi fruit, and cucumbers [17]. The compound is also present in non-dietary plant materials including the heartwood of Venetian sumac (*Cotinus coggygia*, synonym *Rhus cotinus*), the wood of young fustic (*Maclura tinctoria*), *Acacia* species, and *Butea monosperma* (flame-of-the-forest), from which it has historically been extracted as a natural dye. Dietary intake of fisetin in a typical Western diet is estimated at approximately 0.4 mg per day, several orders of magnitude below the pharmacologically active doses studied in preclinical and clinical research [17].

1.4 Synthesis

Fisetin can be obtained by extraction from natural sources (principally *Rhus cotinus* heartwood or strawberry concentrate) or by total chemical synthesis. The Allan-Robinson synthesis is the classical route: condensation of 2-hydroxy-4-methoxyacetophenone with 3,4-dimethoxyphenylglyoxylic acid or the corresponding anhydride under basic conditions, followed by acid-catalyzed demethylation to yield the tetrahydroxyflavone [18]. Modern synthetic routes employ Suzuki coupling, Baker-Venkataraman rearrangement, or Algar-Flynn-Oyamada cyclization strategies. Commercial research-grade fisetin is typically produced by extraction from *Cotinus coggygria* or by semi-synthesis from quercetin precursors, followed by chromatographic purification to greater than 95 percent purity by HPLC. Industrial-scale production for supplement markets utilizes plant extraction (principally from *Rhus succedanea* or *Cotinus coggygria*) with ethanol or ethyl acetate solvent systems and column chromatographic purification.

2. Abstract

Fisetin (3,7,3',4'-tetrahydroxyflavone; CAS 528-48-3) is a plant-derived flavonol polyphenol that has emerged as one of the most pharmacologically versatile dietary flavonoids in contemporary biomedical research. Originally isolated as a yellow pigment from the heartwood of Venetian sumac in 1891 and characterized structurally as a tetrahydroxyflavone in the early twentieth century, the compound attracted limited pharmacological attention until a series of twenty-first-century discoveries established convergent activity across the molecular pathways most intensely studied in aging, neurodegeneration, cancer, and chronic inflammation [1, 2, 6, 9].

The senolytic activity of fisetin was first reported by Zhu et al. (2017) in a screen of flavonoid natural products conducted at the Mayo Clinic Kogod Center on Aging under the direction of James L. Kirkland and Tamara Tchkonja [1]. Among the flavonoids tested, fisetin demonstrated the most potent selective induction of apoptosis in senescent human umbilical vein endothelial cells (HUVECs), with minimal toxicity to proliferating cells. The subsequent Yousefzadeh et al. (2018) study, published in *EBioMedicine*, demonstrated that oral fisetin administered to wild-type C57BL/6 mice beginning at 85 percent of median lifespan (approximately 22 months of age at 500 mg/kg by intermittent gavage) reduced senescence markers (p16Ink4a, p21Cip1, SASP cytokines) in multiple tissues, improved tissue homeostasis, and extended both median and maximum lifespan [2]. This finding positioned fisetin as the first dietary flavonoid with demonstrated gerotherapeutic lifespan extension in a non-genetically-modified mammalian model.

The neuroprotective profile predates the senolytic characterization. The Maher laboratory at the Salk Institute identified fisetin in 2006 as a neurotrophic and neuroprotective flavonol that maintained glutathione levels, activated the ERK pathway, and protected neurons against oxidative and excitotoxic stress in primary hippocampal cultures and in the rabbit ischemic stroke model [6]. Subsequent work demonstrated oral fisetin efficacy in the APPswe/PS1dE9 transgenic Alzheimer's disease mouse model, the MPTP model of Parkinson's disease, and the Huntington's disease R6/2 model [19, 20]. The Maher laboratory further developed CMS121, a fisetin derivative with improved pharmacokinetic properties, which demonstrated

efficacy in Alzheimer's transgenic mice through inhibition of fatty acid synthase (FASN) and reduction of lipid peroxidation, and which completed Phase 1 human clinical testing in 2025 [7, 8].

The anticancer pharmacology spans in vitro and in vivo efficacy in models of prostate, breast, colorectal, lung, melanoma, pancreatic, and bladder cancer. The principal mechanisms include dual inhibition of PI3K/Akt and mTOR signaling (first comprehensively characterized by Khan et al. 2012 in non-small cell lung cancer cells), cell cycle arrest at the G2/M and G1/S checkpoints, induction of mitochondrial apoptosis through modulation of the Bcl-2 family balance, suppression of NF-kappaB-driven survival and inflammatory signaling, inhibition of angiogenesis through VEGF suppression, and reduction of invasiveness through matrix metalloproteinase downregulation [3, 9, 10].

Clinical translation of fisetin is limited by poor oral bioavailability. The compound undergoes rapid and extensive glucuronidation and sulfation in the intestinal epithelium and liver, resulting in low systemic concentrations of the free (unconjugated) aglycone after oral dosing. Multiple clinical trials are nonetheless underway at pharmacological doses (typically 20 mg/kg per day, approximately 1400 mg for a 70 kg individual): the AFFINITY trial (NCT03675724) for frailty in older adults, the STOP-Sepsis trial (NCT05758246) for elderly sepsis patients, and a pilot healthy-volunteer pharmacokinetic trial (NCT06431932) [13, 14]. Formulation approaches including nanocochleates, lipid nanoparticles, and hybrid hydrogels have achieved 10- to 140-fold bioavailability enhancement in preclinical and early-phase human studies [11, 12].

This monograph reviews the complete pharmacological, preclinical, and clinical profile of fisetin, with structured assessment against five alternative senolytic or flavonoid comparators.

3. Discovery and Development History

3.1 Isolation and structural characterization

Fisetin was first isolated from the heartwood of young fustic (Venetian sumac, *Cotinus coggygria*) by Austrian and German chemists in the late nineteenth century. The name derives from the German "Fisetholz" (young fustic wood). The initial isolations characterized fisetin as a yellow plant pigment with dyeing properties; it was used as a natural dye (Natural Brown 1, CI 75620) in textile applications. Structural elucidation proceeded through classical degradation chemistry; the full structure as 3,7,3',4'-tetrahydroxyflavone was confirmed in the early twentieth century through synthesis and spectroscopic comparison [18].

3.2 Early pharmacological characterization

Fisetin attracted limited pharmacological attention through the mid-twentieth century, appearing principally in surveys of flavonoid antioxidant activity and plant polyphenol chemistry. The modern pharmacological era began in the early 2000s when systematic screening of dietary flavonoids for bioactivity in disease-relevant assays identified fisetin as active across multiple targets.

3.3 Neuroprotection discovery (2006 onward)

The Maher laboratory at the Salk Institute published the first comprehensive neuroprotective characterization of fisetin in 2006, demonstrating that the compound promoted differentiation of PC12 cells through activation of the Ras-ERK signaling cascade, maintained intracellular glutathione under oxidative stress, and protected primary hippocampal neurons against glutamate-induced excitotoxicity at low-micromolar concentrations [6]. Subsequent publications extended these findings to *in vivo* models of cerebral ischemia, Alzheimer's disease, Parkinson's disease, and Huntington's disease, establishing fisetin as one of the most broadly neuroprotective dietary flavonoids characterized in preclinical systems [19, 20, 21].

3.4 Senolytic discovery (2017 onward)

The identification of fisetin as a senolytic agent originated from a flavonoid screen conducted at the Mayo Clinic Kogod Center on Aging by Zhu, Tchkonja, Pirtskhalava, and Kirkland, published in *Aging* in 2017 [1]. The screen evaluated a panel of flavonoid natural products for selective cytotoxicity against senescent versus proliferating human umbilical vein endothelial cells. Fisetin was the most potent hit, producing dose-dependent senolytic activity at concentrations of 5 to 20 micromolar. The finding was notable because fisetin had not previously been characterized as a senolytic and because it was substantially more potent in this assay than quercetin, the flavonoid component of the earlier dasatinib-plus-quercetin senolytic combination that had been the primary Kirkland laboratory translational candidate [22].

3.5 Lifespan extension and translational program

The Yousefzadeh et al. (2018) study, conducted as a collaboration between the Kirkland and Niedernhofer laboratories and published in *EBioMedicine*, demonstrated that intermittent oral fisetin (500 mg/kg by gavage, administered on consecutive days monthly) in aged wild-type C57BL/6 mice beginning at 85 percent of median lifespan (approximately 22 months) reduced senescence markers in kidney, liver, and adipose tissue and extended both median and maximum lifespan [2]. The study established fisetin as the first flavonoid with demonstrated lifespan extension in a non-transgenic mammalian model and provided the preclinical basis for the clinical trial program led by the Kirkland laboratory at Mayo Clinic.

3.6 CMS121 development

In parallel with the senolytic program, the Maher laboratory developed CMS121, a synthetic fisetin derivative with improved metabolic stability and oral bioavailability, optimized through iterative medicinal chemistry to maintain neuroprotective potency while reducing susceptibility to phase II conjugation. CMS121 demonstrated efficacy in transgenic Alzheimer's disease mice at oral doses that produced measurable brain concentrations, with a mechanism characterized as inhibition of fatty acid synthase (FASN) and consequent reduction of lipid peroxidation in hippocampal and cortical neurons [7]. CMS121 completed IND-enabling studies and

entered Phase 1 clinical testing in 2024, with results reported in 2025 demonstrating favorable safety, pharmacokinetics, and cardiac safety (QTc assessment) at single doses up to 1800 mg and repeat doses up to 900 mg per day for 7 days [8].

4. Mechanism of Action

Fisetin is a multi-target polyphenol. Its pharmacological activity spans several interconnected molecular pathways, each characterized at the biochemical and cellular level and with varying degrees of in vivo validation. The principal mechanisms are described below in order of translational maturity.

4.1 Senolytic activity and Bcl-2 family modulation

Senescent cells resist apoptosis through upregulation of pro-survival pathways, principally the Bcl-2/Bcl-XL anti-apoptotic protein network and the PI3K/Akt survival axis. Senolytics function by transiently disabling these pro-survival networks, permitting the pro-apoptotic signals that senescent cells themselves generate (through the SASP and through intrinsic DNA damage signaling) to execute apoptosis [22].

Fisetin demonstrates senolytic activity through several convergent mechanisms: (a) direct inhibition of PI3K/Akt survival signaling, reducing Akt-mediated phosphorylation and inactivation of the pro-apoptotic protein Bad; (b) suppression of Bcl-2 and Bcl-XL protein expression and upregulation of Bax, Bak, and Bad pro-apoptotic proteins, tilting the mitochondrial apoptotic balance toward cytochrome c release; (c) activation of caspase-3, caspase-8, and caspase-9 in senescent but not proliferating cells; and (d) suppression of the SASP through NF-kappaB inhibition, reducing the autocrine and paracrine survival signals that sustain senescent cell populations [1, 2, 3].

The senolytic activity is cell-type dependent. Fisetin is robustly senolytic in human umbilical vein endothelial cells (HUVECs) and in murine embryonic fibroblasts, but shows reduced or absent senolytic activity in senescent IMR90 human lung fibroblasts and in primary human preadipocytes [1]. This cell-type specificity likely reflects differential expression of the Bcl-2 family members and of the compensatory survival pathways across cell lineages.

4.2 PI3K/Akt/mTOR pathway inhibition

Fisetin inhibits the PI3K/Akt/mTOR signaling axis at multiple nodes. In non-small cell lung cancer (NSCLC) cells, fisetin reduced protein expression of the PI3K regulatory subunit p85 and catalytic subunit p110, suppressed phosphorylation of Akt at both Thr308 and Ser473, and inhibited mTOR phosphorylation and downstream signaling through p70S6K1, eIF-4E, and 4E-BP1 [3]. The compound additionally increased PTEN protein levels in a dose-dependent manner, reinforcing PI3K/Akt suppression through the canonical PTEN tumor suppressor pathway. In prostate cancer cells, fisetin was characterized as a dual PI3K/mTOR inhibitor that physically interacted with the mTOR kinase domain at two distinct sites, producing direct enzymatic inhibition independent of the upstream PI3K/Akt effects [23].

The mTOR inhibition is reinforced by concurrent AMPK activation. Fisetin increases phosphorylation of AMPKalpha at Thr172, which in turn activates the TSC1/TSC2 complex (the principal endogenous mTOR repressor) through TSC2 phosphorylation, producing convergent mTOR suppression from both the PI3K/Akt (inhibitory) and AMPK (activating TSC2) arms [4, 23].

4.3 SIRT1 activation and NF-kappaB suppression

Fisetin activates SIRT1, a NAD-dependent class III histone deacetylase that occupies a central node in longevity, metabolic regulation, and inflammatory control. SIRT1 activation by fisetin promotes deacetylation of the NF-kappaB p65/RelA subunit at Lys310, suppressing NF-kappaB transcriptional activity and the expression of downstream pro-inflammatory genes including TNF-alpha, IL-1beta, IL-6, COX-2, and iNOS [5, 24]. The SIRT1-mediated NF-kappaB suppression is the principal molecular basis for the anti-SASP activity of fisetin: the senescence-associated secretory phenotype is driven predominantly by NF-kappaB-dependent transcription of inflammatory cytokines, chemokines, and matrix metalloproteinases, and SIRT1 activation directly counteracts this transcriptional program.

SIRT1 activation additionally promotes deacetylation of p53 (reducing p53-dependent cell cycle arrest in non-senescent cells), PGC-1alpha (activating mitochondrial biogenesis), and FOXO transcription factors (promoting stress resistance and autophagy gene expression) [5].

4.4 Nrf2 activation and antioxidant defense

Fisetin induces nuclear translocation of the transcription factor Nrf2 (nuclear factor erythroid 2-related factor 2), which binds to antioxidant response elements (AREs) in the promoters of phase II detoxification and antioxidant defense genes. Downstream targets include heme oxygenase-1 (HO-1), NAD(P)H quinone oxidoreductase 1 (NQO1), glutamate-cysteine ligase (the rate-limiting enzyme in glutathione biosynthesis), glutathione S-transferases, and superoxide dismutase [25]. The Nrf2-mediated maintenance of intracellular glutathione is the principal mechanism underlying the neuroprotective activity characterized by the Maher laboratory, as glutathione depletion is a proximal event in oxidative and excitotoxic neuronal death [6].

4.5 Neuroprotective mechanisms

The neuroprotective pharmacology of fisetin comprises multiple convergent activities: (a) maintenance of intracellular glutathione through Nrf2-mediated upregulation of glutathione biosynthetic enzymes; (b) activation of the Ras-ERK-CREB signaling cascade, promoting expression of neurotrophic factors including brain-derived neurotrophic factor (BDNF); (c) inhibition of lipoxygenase (5-LOX and 12-LOX) and reduction of lipid peroxidation products; (d) suppression of microglial activation and neuroinflammatory cytokine release through NF-kappaB inhibition; and (e) inhibition of fatty acid synthase (FASN), the mechanism principally characterized for the derivative CMS121, which reduces de novo lipogenesis and consequent lipid peroxidation in hippocampal neurons [6, 7, 19].

In the APPswe/PS1dE9 transgenic Alzheimer's mouse model, oral fisetin (25 mg/kg per day for 3 to 9 months) prevented cognitive decline on the Morris water maze and the contextual fear conditioning paradigm, reduced hippocampal inflammation, and attenuated markers of oxidative stress without affecting amyloid plaque burden, suggesting that the neuroprotective mechanism operates downstream of amyloid deposition [19].

4.6 Anticancer mechanisms

Fisetin induces cell cycle arrest and apoptosis across a broad range of cancer cell types. The principal mechanisms include: (a) G2/M and G1/S cell cycle arrest through upregulation of p21Cip1 and p27Kip1 and downregulation of cyclins D1,

B1, and A2; (b) induction of mitochondrial (intrinsic) apoptosis through Bax/Bak upregulation, Bcl-2/Bcl-XL downregulation, cytochrome c release, and caspase-9 and caspase-3 activation; (c) activation of the extrinsic (death receptor) apoptotic pathway through TRAIL sensitization and caspase-8 activation; (d) suppression of NF-kappaB-driven survival signaling; (e) inhibition of Wnt/beta-catenin signaling (characterized in colorectal cancer models through TCF4-beta-catenin transcriptional activity suppression); (f) anti-angiogenic activity through VEGF and HIF-1alpha suppression; and (g) anti-metastatic activity through MMP-2 and MMP-9 downregulation and inhibition of epithelial-mesenchymal transition [9, 10, 26].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption and bioavailability

Fisetin is poorly bioavailable after oral administration. The compound has low aqueous solubility (approximately 10 micrograms per milliliter) and undergoes extensive first-pass metabolism in the intestinal epithelium and liver, principally through glucuronidation by uridine 5'-diphospho-glucuronosyltransferases (UGTs, principally UGT1A1 and UGT1A3) and sulfation by sulfotransferases (SULTs, principally SULT1A1 and SULT1A3) [11, 27]. In rat pharmacokinetic studies, oral bioavailability of the free (unconjugated) aglycone is approximately 44 percent by total flavonoid measurement (including conjugated metabolites) but substantially lower by free aglycone measurement, as the majority of circulating fisetin equivalents are glucuronide and sulfate conjugates with uncertain pharmacological activity [27].

In a human pharmacokinetic study of 15 healthy volunteers receiving a single 1000 mg oral dose of unformulated fisetin, plasma concentrations of the free aglycone were low and variable, with rapid appearance of glucuronide and sulfate conjugates [12]. The hybrid-hydrogel formulation (FF-20) produced approximately 24-fold higher peak plasma concentration (C_{max}) and 47-fold higher area under the curve (AUC) compared to unformulated fisetin in the same crossover design [12].

5.2 Distribution

Fisetin distributes into tissues following oral absorption. In rodent studies, the compound crosses the blood-brain barrier in measurable quantities, as demonstrated by brain tissue concentration measurements following oral dosing and by the documented central nervous system pharmacological effects (cognitive improvement in Alzheimer's transgenic mice, neuroprotection in ischemia models) [6, 19]. Plasma protein binding has not been precisely characterized in published human studies but is expected to be moderate to high, consistent with the flavonol class.

5.3 Metabolism

Fisetin undergoes extensive phase II metabolism. The principal metabolic transformations are: (a) glucuronidation at the 3, 7, 3', and 4' hydroxyl positions by hepatic and intestinal UGTs; (b) sulfation at the same positions by SULTs; (c) methylation of the catechol B-ring by catechol-O-methyltransferase (COMT) to produce geraldol (3'-O-methylfisetin, also known as 3,7,4'-trihydroxy-3'-methoxyflavone), the principal methylated metabolite; and (d) further glucuronidation and sulfation of geraldol [27, 28]. Phase I oxidative metabolism by cytochrome P450 enzymes is a minor pathway; fisetin does not appear to be a potent inhibitor or inducer of the major CYP isoforms at dietary concentrations, though inhibition of CYP1A2, CYP2C9, and CYP3A4 has been reported at high in vitro concentrations [28].

The pharmacological activity of the conjugated metabolites is incompletely characterized. Some glucuronide and sulfate conjugates retain modest activity at the targets of the parent compound, and tissue-specific deconjugation by beta-glucuronidase (expressed at elevated levels in inflamed tissues and in the tumor microenvironment) may regenerate the active aglycone at the site of action. This "deconjugation hypothesis" is invoked to explain the disconnect between the low systemic free aglycone concentrations and the pharmacological effects observed at oral doses in clinical and preclinical studies [28].

5.4 Elimination

Fisetin metabolites are eliminated principally through renal excretion of the glucuronide and sulfate conjugates, with a smaller biliary excretion component. The plasma elimination half-life of the free aglycone in rodent studies is approximately 1 to 3 hours after intravenous dosing; the effective half-life after oral dosing is longer owing to the sustained absorption phase and the contribution from entero-hepatic recirculation of conjugated metabolites [27].

5.5 Routes of administration

Oral administration is the principal route in both preclinical and clinical research. The compound is supplied as a powder (for animal gavage or human capsule/tablet formulation) or as a solution in DMSO or ethanol (for in vitro studies). Intraperitoneal injection is used in rodent studies when rapid systemic exposure is required. Intravenous administration has been used in preclinical pharmacoki-

netic studies but is not a standard clinical route owing to the poor aqueous solubility. Topical application has been studied in dermatological and skin cancer models [29].

5.6 Formulation strategies for bioavailability enhancement

Multiple formulation approaches have been developed to overcome the bioavailability limitation:

Nanocochleates: Fisetin-loaded nanocochleates (lipid-based cylindrical nanostructures) produced a 141-fold increase in oral bioavailability compared to free fisetin in mouse pharmacokinetic studies, the largest enhancement reported to date [11].

Liposomes: Liposomal fisetin formulations produced approximately 5- to 20-fold bioavailability enhancement in preclinical studies, with improved aqueous dispersibility and protection from degradation in the gastrointestinal tract.

Nanoemulsions and self-nanoemulsifying drug delivery systems (SNEDDS): Oil-in-water nanoemulsions incorporating fisetin produced enhanced solubilization and bioavailability in rodent studies.

Hybrid hydrogels: The FF-20 hybrid-hydrogel formulation produced 47-fold AUC enhancement in the human pharmacokinetic crossover study referenced above [12].

Polymeric nanoparticles: PLGA and chitosan-based nanoparticles loaded with fisetin have demonstrated sustained release and improved bioavailability in preclinical models.

The choice of formulation for research applications depends on the route of administration, the target tissue, and the required duration of exposure. For senolytic applications at the high acute doses (20 mg/kg) used in clinical trials, unformulated fisetin in capsule form remains the standard owing to the intermittent dosing schedule and the tolerability demonstrated in early clinical studies [13, 14].

6. Preclinical Pharmacology

6.1 Aging and cellular senescence

The preclinical evidence for fisetin in aging biology is anchored by two principal studies. The Zhu et al. (2017) in vitro screen demonstrated selective senolytic activity in senescent HUVECs at 5 to 20 micromolar concentrations, with a therapeutic window (senolytic versus cytotoxic to proliferating cells) of approximately 5- to 10-fold [1]. The Yousefzadeh et al. (2018) in vivo study demonstrated that intermittent oral fisetin (500 mg/kg on 2 consecutive days, monthly) in aged wild-type C57BL/6 mice beginning at 85 percent of median lifespan (approximately 22 months) reduced senescence-associated beta-galactosidase staining and p16Ink4a and p21Cip1 mRNA expression in kidney, liver, and adipose tissue; reduced circulating SASP cytokines (IL-6, TNF-alpha, MCP-1); improved physical function (grip strength, treadmill endurance); and extended both median lifespan (by approximately 10 percent) and maximum lifespan [2].

Additional preclinical studies have demonstrated that fisetin reduces senescent cell burden in models of radiation-induced senescence, chemotherapy-induced senescence, and replicative senescence in culture-expanded human adipose-derived stem cells [30].

6.2 Neurodegeneration

Fisetin has been characterized in multiple preclinical models of neurodegeneration:

Alzheimer's disease: In the APPswe/PS1dE9 double-transgenic mouse model, oral fisetin at 25 mg/kg per day for 3 to 9 months prevented the decline in cognitive performance, reduced markers of oxidative stress and inflammation in the hippocampus, and decreased the levels of carbonylated proteins without significantly altering amyloid plaque load [19]. In the 3xTg-AD mouse model, fisetin prevented synaptic dysfunction and preserved hippocampal long-term potentiation [21].

Parkinson's disease: In the MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) mouse model, fisetin pretreatment attenuated dopaminergic neuron loss in the substantia nigra, reduced striatal dopamine depletion, and improved motor function on the rotarod test [20].

Huntington's disease: In the R6/2 transgenic Huntington's disease mouse model, fisetin extended survival and delayed motor symptom onset when administered from early in the disease course [21].

Stroke: In the rabbit small clot embolism model of ischemic stroke, intravenous fisetin reduced infarct volume and improved neurological outcome when administered within hours of the ischemic event [6].

Traumatic brain injury: Fisetin has demonstrated neuroprotective effects in rodent models of controlled cortical impact, reducing neuroinflammation and improving cognitive outcomes on the Morris water maze [31].

6.3 Cancer

The anticancer pharmacology of fisetin has been characterized across multiple tumor types in vitro and in vivo:

Prostate cancer: Fisetin inhibited growth and induced apoptosis in both androgen-dependent (LNCaP) and androgen-independent (PC-3, DU145) prostate cancer cell lines. In the TRAMP (transgenic adenocarcinoma of the mouse prostate) model, oral fisetin at 1 mg per mouse per day for 8 weeks reduced tumor volume, decreased serum insulin-like growth factor-1 (IGF-1), and suppressed markers of proliferation and angiogenesis [23, 32].

Breast cancer: Fisetin suppressed proliferation of MCF-7 and MDA-MB-231 breast cancer cells and inhibited mammary tumor growth and metastasis in the 4T1 syngeneic mouse model through PI3K/Akt/mTOR pathway inhibition [10, 33].

Colorectal cancer: Fisetin inhibited Wnt/beta-catenin signaling in colorectal cancer cell lines and reduced tumor growth in xenograft models [26].

Lung cancer: Dual PI3K/Akt and mTOR inhibition was comprehensively characterized in A549 and H1299 NSCLC cells, with in vivo efficacy in xenograft models [3].

Melanoma: Fisetin reduced invasion and migration of melanoma cells through MMP downregulation and induced mitochondrial apoptosis in A375 and SK-MEL-28 cell lines [9].

Pancreatic cancer: Fisetin induced apoptosis and suppressed NF-kappaB activation in pancreatic cancer cell lines [9].

6.4 Inflammation

Fisetin has demonstrated anti-inflammatory activity in models of acute and chronic inflammation, including lipopolysaccharide (LPS)-induced sepsis models, carrageenan-induced paw edema, collagen-induced arthritis, DSS-induced colitis, and allergic asthma. The principal mechanism is NF-kappaB suppression through the SIRT1-mediated and direct IKK-inhibitory pathways, with additional contributions from COX-2 suppression, iNOS inhibition, and reduction of pro-inflammatory cytokine release [5, 24].

6.5 Metabolic disease

Fisetin has demonstrated anti-diabetic and anti-obesity effects in preclinical models. In high-fat-diet-induced obesity mouse models, fisetin reduced body weight gain, improved glucose tolerance, decreased hepatic steatosis, and improved insulin sensitivity, principally through AMPK activation and SIRT1-mediated metabolic regulation [34]. In streptozotocin-induced diabetic rats, fisetin reduced blood glucose, improved antioxidant status, and attenuated diabetic nephropathy [35].

7. Clinical Evidence Base

7.1 Senolytic clinical trials

The clinical development of fisetin as a senolytic agent is led by the Kirkland laboratory at Mayo Clinic. Multiple clinical trials are registered on ClinicalTrials.gov:

AFFINITY trial (NCT03675724): "Alleviation by Fisetin of Frailty, Inflammation, and Related measures in Older Adults." A Phase 2 randomized, double-blind, placebo-controlled trial of oral fisetin at 20 mg/kg per day for 2 consecutive days (repeated monthly for 2 months) in older adults (age 70 and older) with frailty. The primary endpoints are change in gait speed and markers of senescence (p16Ink4a, SASP cytokines) [13]. The trial has completed enrollment; results have not been published in a peer-reviewed journal as of the most recent monograph revision.

COVID-19 in skilled nursing facilities (NCT04537299 and NCT04476953): Two trials evaluated fisetin at 20 mg/kg per day for 2 consecutive days in elderly residents of skilled nursing facilities during the COVID-19 pandemic, based on the hypothesis that senescent cell burden contributes to the increased severity of SARS-CoV-2 infection in older adults. Among 44 patients who received fisetin intervention in a 536-patient study, 64 percent reported significant alleviation of symptoms including fatigue, muscle pain, and orthostatic hypotension [14, 36].

STOP-Sepsis (NCT05758246): A multicenter, randomized, double-blind, adaptive-allocation Phase 2 trial evaluating fisetin (single oral dose of 20 mg/kg, or two oral doses of 20 mg/kg spaced 1 day apart, versus placebo) in 220 elderly patients (age greater than 65) with sepsis. The trial is based on the hypothesis that acute senolytic intervention reduces the senescent cell-mediated inflammatory amplification that drives clinical deterioration in elderly sepsis [14].

Healthy volunteer pharmacokinetics (NCT06431932): A pilot trial evaluating fisetin pharmacokinetics, safety, and biomarker effects in healthy volunteers.

7.2 Neuroprotection clinical development

The principal clinical path for fisetin neuroprotection is through the derivative CMS121, developed by the Maher laboratory and advanced by Virogenics (San Diego). CMS121 completed Phase 1 clinical testing in 2024 to 2025. Single ascending doses of 100, 300, 600, 1200, and 1800 mg and multiple ascending doses of 300, 600, and 900 mg per day for 7 days were evaluated in healthy adult volunteers. The compound was generally well tolerated, with the majority of adverse events mild in severity (headache, nausea, dizziness). Pharmacokinetic parameters were consistent with once- or twice-daily oral dosing. No clinically significant QTc prolongation was observed at any dose [8]. Phase 2 trials in mild cognitive impairment and Alzheimer's disease are planned.

Fisetin itself has not been evaluated in dedicated neurodegeneration clinical trials. The preclinical neuroprotective evidence supports investigation, but the bioavailability limitations of the parent compound have directed clinical neuroprotection development toward the CMS121 derivative.

7.3 Cancer clinical development

Fisetin has not been evaluated in dedicated oncology clinical trials as of the most recent monograph revision. The preclinical evidence base is extensive but has not yet produced a clinical development program. The bioavailability limitation and the absence of patent protection (as a natural product) are the principal barriers to oncology clinical development.

7.4 Other clinical applications

A small number of clinical studies have evaluated fisetin in inflammatory and metabolic conditions. These are principally small open-label studies or pilot trials; none has produced registration-quality evidence. The clinical translation of fisetin beyond the senolytic and neuroprotective (CMS121) programs remains early-stage.

8. Sourcing and Quality Verification

Fisetin is commercially available from multiple sources at research and supplement grades.

Research-grade supply: Sigma-Aldrich, Cayman Chemical, Tocris, MedChemExpress, Selleckchem, TCI Chemicals, and other research chemical suppliers provide fisetin at greater than 95 percent purity (typically greater than 98 percent by HPLC) in milligram to gram quantities. Pricing is approximately \$20 to \$80 per gram at research grade. The compound is supplied as the free aglycone (not a salt form); it is a yellow to orange crystalline powder.

Supplement-grade supply: Multiple dietary supplement manufacturers supply fisetin capsules at doses of 100 to 500 mg per capsule, typically sourced from plant extraction (*Rhus succedanea*, *Cotinus coggygia*, or synthetic). Supplement-grade material varies in purity and may contain other flavonoids, plant matrix components, or excipients. Investigators using supplement-grade material for research should confirm purity by independent analysis.

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 (287.0556 for [M+H]⁺ by electrospray ionization)
- Ultraviolet-visible spectrophotometry confirming characteristic absorption maxima at approximately 320 and 360 nm
- Karl Fischer or loss-on-drying analysis for residual water content
- Residual solvent analysis by gas chromatography if the supplier uses organic solvents in purification

Third-party analytical confirmation is appropriate for supplement-grade material and recommended for research-grade material when dose-response precision is critical. The fisetin market includes both high-quality suppliers and lower-quality

sources where purity may not match the certificate of analysis; on-receipt verification is standard practice.

9. Reconstitution and Handling

Fisetin is sparingly soluble in water and is typically handled in organic solvent for research applications.

Stock solution preparation: Dissolve fisetin in dimethyl sulfoxide (DMSO) at concentrations of 50 to 100 mM (approximately 14 to 29 mg/mL). The compound dissolves readily in DMSO with brief vortexing. Stock solutions in DMSO are stable at minus 20 degrees Celsius for at least 6 months when protected from light and moisture. For aqueous applications, the DMSO stock can be diluted into aqueous buffer; the final DMSO concentration should not exceed 0.1 to 0.5 percent (v/v) for cell culture applications to avoid solvent toxicity.

Alternative solvents: Fisetin dissolves in ethanol and methanol at concentrations of approximately 10 to 20 mg/mL. Ethanol-based stocks are appropriate for in vivo gavage formulations (typically diluted in corn oil, olive oil, or aqueous vehicle) and for in vitro applications where DMSO is undesirable.

Aqueous formulations for in vivo use: For oral gavage in rodent studies, fisetin is typically suspended in 5 percent carboxymethylcellulose or in peanut oil/corn oil. For the senolytic dosing regimen (500 mg/kg in mouse studies), the compound is administered as a concentrated suspension by oral gavage.

Storage: Solid fisetin should be stored at minus 20 degrees Celsius or at 2 to 8 degrees Celsius in a desiccated container protected from light. The compound is sensitive to oxidation (owing to the catechol B-ring) and to photodegradation; storage under inert gas (nitrogen or argon) is recommended for long-term archival of analytical reference standards.

Stability considerations: Fisetin is susceptible to oxidative degradation in alkaline aqueous solutions; working solutions should be prepared at neutral pH and used within 24 hours for in vitro applications. The compound is stable in acidic conditions (pH 2 to 5) and in organic solvent.

10. Stack Interactions and Combinations

Investigators conducting research with fisetin in combination with other compounds should consider the following interactions:

Other senolytics (dasatinib, quercetin, navitoclax): The combination of fisetin with other senolytic agents has not been extensively characterized but is mechanistically plausible. Dasatinib plus quercetin (D+Q) is the most clinically advanced senolytic combination; fisetin could theoretically substitute for or supplement quercetin in this combination, though the Bcl-2 family selectivity profile differs. Additive or synergistic senolytic effects are possible, but additive toxicity to normal cells should be monitored.

Quercetin: Fisetin and quercetin are structurally related flavonols (fisetin is 5-deoxyquercetin) and share multiple molecular targets. Co-administration may produce additive effects on PI3K/Akt/mTOR inhibition, NF-kappaB suppression, and antioxidant defense. Both compounds compete for the same phase II conjugation enzymes (UGTs, SULTs), and co-administration may modestly increase the bioavailability of each by saturating the conjugation capacity, though this has not been formally demonstrated in human pharmacokinetic studies.

Rapamycin and mTOR inhibitors: Fisetin and rapamycin converge on mTOR inhibition. The combination has been studied in preclinical cancer models and may produce synergistic growth inhibition. Investigators using fisetin in combination with rapamycin or rapalogs (everolimus, temsirolimus) should monitor for additive immunosuppression and metabolic effects.

Metformin and AMPK activators: Fisetin activates AMPK; metformin is the canonical AMPK activator with established gerotherapeutic research interest. The combination is mechanistically coherent for aging and metabolic research applications. Additive AMPK activation should be expected; additive gastrointestinal effects (metformin-induced diarrhea, fisetin-induced nausea at high doses) may occur.

Curcumin and other polyphenols: Co-administration of fisetin with curcumin, resveratrol, EGCG, or other dietary polyphenols may produce additive or overlapping effects on NF-kappaB, Nrf2, and SIRT1 pathways. Competition for phase II conjugation enzymes is expected. The combinations have not been formally characterized in clinical pharmacokinetic studies.

Phase II metabolism modulators: Compounds that inhibit UGT or SULT enzymes (probenecid, some nonsteroidal anti-inflammatory drugs) may increase fisetin bioavailability by reducing first-pass conjugation. Piperine (the alkaloid from black pepper) is a broad-spectrum UGT inhibitor that has been shown to increase the bioavailability of several polyphenols and is commonly co-formulated with flavonoid supplements for this purpose.

CYP substrates: Fisetin has been reported to inhibit CYP1A2, CYP2C9, and CYP3A4 at high in vitro concentrations. Clinically relevant CYP inhibition at the systemic concentrations achieved by oral dosing of the unformulated compound is unlikely but should be considered with high-bioavailability formulations or with chronic high-dose regimens.

Anticoagulants: Fisetin has been reported to inhibit platelet aggregation in vitro. Concurrent use with warfarin, heparin, or direct oral anticoagulants should be approached with awareness of potential additive anticoagulant effects, though clinical bleeding events attributable to fisetin have not been reported.

11. Adverse Events and Safety

11.1 Preclinical safety

Fisetin has demonstrated a favorable safety profile in preclinical studies. In rodent toxicity studies, oral doses up to 2000 mg/kg (acute, single dose) and up to 500 mg/kg per day (chronic, intermittent dosing for months) have been well tolerated without evidence of major organ toxicity, hematological abnormality, or reproductive toxicity [2, 37]. The LD50 in mice has not been precisely determined but exceeds 2000 mg/kg by oral administration, placing the compound in the low-toxicity category by Globally Harmonized System classification.

11.2 Human clinical safety

Clinical safety data for fisetin are derived from the Mayo Clinic senolytic trials and from the healthy-volunteer pharmacokinetic studies. At the 20 mg/kg oral dose (approximately 1400 mg for a 70 kg individual, administered as 2 consecutive daily doses), fisetin has been generally well tolerated. Reported adverse events include:

- Mild gastrointestinal symptoms (nausea, diarrhea, abdominal discomfort) in a minority of participants
- Mild headache
- No serious adverse events attributable to fisetin have been reported in published trial data

The CMS121 Phase 1 data (at doses up to 1800 mg single and 900 mg per day repeated) similarly demonstrated acceptable tolerability with predominantly mild adverse events and no clinically significant QTc prolongation [8].

11.3 Theoretical safety considerations

Catechol toxicity: The catechol (ortho-dihydroxyphenyl) moiety on the fisetin B-ring can undergo oxidation to a reactive ortho-quinone intermediate, which can form covalent adducts with protein thiols. This mechanism has been implicated in the toxicity of other catechol-containing compounds (dopamine metabolites, EGCG

at very high doses). At the doses used in clinical senolytic studies, this risk appears to be low, but chronic high-dose administration should be monitored for hepatic and renal safety signals.

Iron chelation: Fisetin, like other flavonols, chelates transition metal ions (iron, copper). This property contributes to the antioxidant activity but may theoretically reduce iron bioavailability with chronic high-dose co-administration with dietary iron. Clinical significance has not been established.

Thyroid effects: Some flavonoids inhibit thyroid peroxidase activity at high concentrations. Thyroid function effects of chronic high-dose fisetin have not been characterized in humans and should be monitored in long-term studies.

11.4 Supplement safety context

Fisetin is commercially available as a dietary supplement in the United States and is generally recognized as safe at supplement doses (100 to 500 mg per day). The safety profile at these doses is supported by the long history of dietary exposure through strawberry and fruit consumption and by the supplement market experience, though formal clinical safety studies at chronic supplement doses have not been published.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five senolytic, flavonoid, or neuroprotective candidates against fisetin, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile (clinical or preclinical), and overall validation. The five candidates were selected as the principal compounds that share one or more of fisetin's target profiles (senolytic activity, flavonoid neuroprotection, or polyphenol-mediated PI3K/mTOR inhibition) and that have substantive preclinical or clinical evidence.

12.1 Quercetin (in combination with dasatinib)

Mechanism: Quercetin is a flavonol structurally related to fisetin (fisetin is 5-deoxy-quercetin). As a senolytic, quercetin is used in combination with dasatinib (a tyrosine kinase inhibitor); the combination (D+Q) produces synergistic senolytic activity through concurrent inhibition of multiple senescent cell anti-apoptotic pathways (SRC kinases, PI3K/Akt, Bcl-2/Bcl-XL, p21, PAI-1, serpins) [22, 38].

Development trajectory: The D+Q combination was the first senolytic regimen advanced to human clinical testing by the Kirkland laboratory. Phase 1 and Phase 2 clinical trials have been completed in diabetic kidney disease (NCT02848131), idiopathic pulmonary fibrosis (NCT02874989), and osteoporosis (NCT04313634). The diabetic kidney disease trial (Hickson et al. 2019) demonstrated reduction of adipose tissue senescent cell burden and circulating SASP factors after 3 days of D+Q treatment [38].

Novelty: Moderate. The D+Q combination was the pioneering clinical senolytic regimen but is now well established in the field. Quercetin alone is a common dietary supplement with no novelty as a single agent.

Effect size: The D+Q combination has produced measurable reductions in senescent cell markers in human clinical trials. Quercetin alone has weaker senolytic activity than fisetin in the HUVEC senolytic assay; the combination with dasatinib is required for robust clinical-level senolytic activity [22].

Promising potential: Moderate to high. The D+Q combination has the most advanced clinical development program among senolytic regimens, with multiple completed Phase 1 and Phase 2 trials and positive biomarker data. Dasatinib is an FDA-approved oncology drug, providing a defined safety and pharmacokinetic profile for the combination partner. However, the requirement for a prescription tyrosine kinase inhibitor limits accessibility compared to single-agent fisetin.

Side-effect profile: Dasatinib carries known risks including pleural effusion, cytopenias, hepatotoxicity, and QT prolongation. In the short-duration senolytic dosing regimen (3 days), the D+Q combination has been well tolerated, but the dasatinib component introduces a risk profile absent from single-agent fisetin. Quercetin alone is well tolerated at supplement doses.

Overall validation: High. The D+Q combination is the most clinically validated senolytic regimen, with human biomarker evidence of senescent cell clearance and favorable short-term tolerability. Quercetin alone is less validated as a senolytic than fisetin.

Comparison to fisetin: Fisetin has the advantage of single-agent senolytic activity without the requirement for a prescription tyrosine kinase inhibitor, simpler dosing, better supplement-market accessibility, and a multi-target pharmacology that extends beyond senolysis to neuroprotection and cancer chemoprevention. The D+Q combination has the advantage of more advanced clinical development, greater potency as a senolytic combination, and the well-characterized pharmacokinetic profile of dasatinib. The two regimens are likely to occupy complementary positions in the translational senolytic landscape, with D+Q for clinical applications where maximal senolytic potency is required and fisetin for broader gerotherapeutic applications where single-agent simplicity, safety, and multi-pathway activity are valued.

12.2 Navitoclax (ABT-263)

Mechanism: Navitoclax is a small-molecule inhibitor of the Bcl-2 family anti-apoptotic proteins Bcl-2, Bcl-XL, and Bcl-w, originally developed as an anticancer agent by Abbott Laboratories (now AbbVie). Its senolytic activity derives from direct pharmacological inhibition of the Bcl-2/Bcl-XL pro-survival network that maintains senescent cell viability [39].

Development trajectory: Navitoclax was developed through Phase 2 clinical trials for chronic lymphocytic leukemia and other hematological malignancies before being superseded by venetoclax (a Bcl-2-selective inhibitor with reduced platelet toxicity). The senolytic application was characterized by the Kirkland and van Deursen laboratories; navitoclax is a potent senolytic across multiple cell types but has not been advanced to dedicated senolytic clinical trials owing to its dose-limiting thrombocytopenia [39].

Novelty: Low in the oncology context; moderate in the senolytic context as a mechanistic probe of Bcl-2/Bcl-XL-dependent senescent cell survival.

Effect size: High. Navitoclax is one of the most potent senolytics characterized, producing near-complete clearance of senescent cells in vitro and substantial reduction in vivo in multiple preclinical models.

Promising potential: Low for senolytic clinical translation owing to thrombocytopenia. The compound is a valuable research tool for understanding Bcl-2 family-dependent senescent cell survival but is unlikely to advance as a clinical senolytic agent in its current form. Prodrug and targeted-delivery strategies are under investigation.

Side-effect profile: Dose-limiting thrombocytopenia (due to Bcl-XL inhibition in platelets) is the principal safety concern and the barrier to clinical senolytic development. Additional adverse events include neutropenia, gastrointestinal toxicity, and fatigue [39].

Overall validation: Moderate as a senolytic (strong preclinical, no dedicated senolytic clinical trials). High as an anticancer agent (Phase 2 clinical data in hematological malignancies).

Comparison to fisetin: Navitoclax is substantially more potent as a senolytic than fisetin but has a prohibitive safety profile for the gerotherapeutic applications (chronic or intermittent use in elderly populations) that are the principal clinical context for senolytic therapy. Fisetin has the advantages of a favorable safety profile, oral supplement availability, multi-target pharmacology, and applicability to the aging and frailty populations that are the primary senolytic clinical market. The two compounds represent opposite ends of the potency-safety spectrum in the senolytic class.

12.3 Resveratrol

Mechanism: Resveratrol (3,5,4'-trihydroxy-trans-stilbene) is a stilbenoid polyphenol produced by several plants in response to injury or pathogen attack, found at highest concentration in the skin of red grapes and in red wine. Like fisetin, resveratrol activates SIRT1, inhibits NF-kappaB, modulates PI3K/Akt/mTOR signaling, and has been characterized as neuroprotective, cardioprotective, and anti-inflammatory in preclinical models [40].

Development trajectory: Resveratrol has been the subject of extensive preclinical and clinical investigation for over two decades. Multiple clinical trials have evaluated resveratrol for cardiovascular disease, diabetes, cancer prevention, and neurodegeneration. Results have been mixed, with modest effects in some trials and null results in others. The bioavailability limitation (rapid glucuronidation and sulfation, similar to fisetin) has been identified as a principal barrier to clinical translation [40].

Novelty: Low. Resveratrol is the most extensively studied dietary polyphenol and is well characterized at the molecular, preclinical, and clinical levels.

Effect size: Mixed. Preclinical effect sizes are consistently moderate to large across anti-inflammatory, antioxidant, and metabolic endpoints. Clinical effect sizes have been small and inconsistent, with the possible exception of metabolic endpoints in diabetic patients.

Promising potential: Low to moderate. Despite extensive research investment, resveratrol has not produced a registered clinical indication or a definitive positive large-scale clinical trial. The compound persists as a widely used dietary supplement.

Side-effect profile: Well tolerated at supplement doses (up to 1000 mg per day). Gastrointestinal adverse events (diarrhea, nausea) at higher doses. No serious safety concerns at typical supplement doses.

Overall validation: Moderate. The research literature is the largest of any dietary polyphenol, but clinical translation has been disappointing relative to the preclinical promise.

Comparison to fisetin: Fisetin and resveratrol share multiple molecular targets (SIRT1, NF-kappaB, PI3K/mTOR) and face the same bioavailability challenges. Fisetin has the advantage of more potent senolytic activity (resveratrol is not char-

acterized as a robust senolytic), the specific neuroprotective profile characterized by the Maher laboratory and advanced through CMS121, and a more favorable position in the current translational landscape (active Mayo Clinic clinical trials with defined senolytic endpoints). Resveratrol has the advantage of a vastly larger research literature, more extensive human safety data, and broader public recognition. The two compounds are mechanistically overlapping but have diverged in their clinical positioning, with fisetin now positioned primarily as a senolytic and neuroprotective candidate and resveratrol positioned primarily as a cardiovascular and metabolic supplement.

12.4 Luteolin

Mechanism: Luteolin (3',4',5,7-tetrahydroxyflavone) is a flavone (not a flavonol; it lacks the 3-hydroxyl group that defines the flavonol subclass) found in celery, parsley, broccoli, and other vegetables. Luteolin shares multiple targets with fisetin including NF-kappaB suppression, PI3K/Akt inhibition, Nrf2 activation, and anti-inflammatory activity. It has been characterized as neuroprotective in multiple pre-clinical models [41].

Development trajectory: Luteolin has been studied preclinically for neuroprotection, cancer chemoprevention, and anti-inflammatory activity. Clinical development is limited; a small number of clinical trials have evaluated luteolin (often in combination with other flavonoids) for neuroinflammatory conditions including autism spectrum disorder (as a formulated supplement, NeuroProtek). No clinical trials evaluate luteolin as a senolytic [41].

Novelty: Low. The compound is well characterized as a dietary flavone.

Effect size: Moderate in preclinical anti-inflammatory and neuroprotective models. Limited clinical effect-size data.

Promising potential: Low. No active clinical development program for major indications. The compound is available as a dietary supplement.

Side-effect profile: Well tolerated at dietary and supplement doses. No serious safety concerns reported.

Overall validation: Low to moderate. Preclinical evidence is substantial; clinical evidence is minimal.

Comparison to fisetin: Fisetin has substantially more advanced clinical development (active Mayo Clinic senolytic trials, CMS121 Phase 1 completed), more potent senolytic activity, and a more defined translational pathway. Luteolin has a comparable anti-inflammatory and neuroprotective preclinical profile but has not been developed as aggressively. The two compounds share overlapping but not identical target profiles (luteolin has 5-hydroxyl-dependent interactions absent from fisetin; fisetin has 3-hydroxyl-dependent flavonol chemistry absent from luteolin).

12.5 EGCG (Epigallocatechin gallate)

Mechanism: EGCG is a catechin polyphenol and the most abundant bioactive compound in green tea (*Camellia sinensis*). EGCG inhibits PI3K/Akt/mTOR, activates AMPK, suppresses NF-kappaB, modulates Nrf2, inhibits telomerase in cancer cells, and has been characterized as anti-inflammatory, antioxidant, and chemopreventive [42].

Development trajectory: EGCG has been the subject of extensive clinical investigation for cancer prevention (prostate, breast, colorectal), cardiovascular disease, obesity, and neurodegeneration. The Sunphenon green tea extract has been evaluated in multiple clinical trials. Results have been mixed, with modest chemopreventive signals in some studies but no definitive registration-quality evidence for a specific clinical indication [42].

Novelty: Low. EGCG is the most extensively studied tea polyphenol.

Effect size: Mixed. Epidemiological data suggest modest cancer-preventive effects associated with green tea consumption; interventional clinical trials have produced small and inconsistent effects. Preclinical effect sizes are moderate to large.

Promising potential: Low to moderate. Despite decades of research, EGCG has not produced a registered clinical indication. Liver toxicity at high supplement doses (exceeding 800 mg per day) has emerged as a safety concern that limits dose escalation [42].

Side-effect profile: Generally well tolerated at moderate doses (300 to 500 mg per day). Hepatotoxicity has been reported at high doses (greater than 800 mg per day), with cases of severe liver injury requiring hospitalization. This is the principal safety difference from fisetin, which has not demonstrated hepatotoxic potential at the doses studied [42].

Overall validation: Moderate. The research literature is extensive, but clinical translation has been limited by bioavailability, mixed clinical results, and the hepatotoxicity signal at high doses.

Comparison to fisetin: Fisetin and EGCG share multiple molecular targets and face similar bioavailability limitations. Fisetin has the advantages of defined senolytic activity (EGCG is not characterized as senolytic), a more favorable safety profile at high doses (no hepatotoxicity signal), and active clinical development in senolytic indications. EGCG has the advantages of a larger research literature, more extensive epidemiological data, and broader public awareness through the green tea association. The fisetin safety and senolytic profile positions it more favorably for the gerotherapeutic applications that represent the most active translational frontier.

12.6 Comparator summary

The five comparators occupy distinct positions in the polyphenol and senolytic pharmacology landscape. **Dasatinib plus quercetin** is the most clinically advanced senolytic regimen, with human biomarker evidence, but requires a prescription oncology drug as a combination partner. **Navitoclax** is the most potent senolytic characterized but has a prohibitive thrombocytopenia risk for gerotherapeutic applications. **Resveratrol** is the most extensively studied dietary polyphenol but has produced disappointing clinical translation despite decades of research and is not senolytic. **Luteolin** shares anti-inflammatory and neuroprotective targets but has minimal clinical development. **EGCG** has the largest research literature among tea polyphenols but carries a hepatotoxicity risk at high doses and is not senolytic.

Fisetin occupies a distinctive position in this comparator landscape: it is the only compound with demonstrated single-agent senolytic activity, lifespan extension in wild-type mice, an active clinical trial program in senolytic indications, a defined neuroprotective profile advanced through a clinical-stage derivative (CMS121), a favorable high-dose safety profile, and broad multi-pathway pharmacology spanning aging, neurodegeneration, cancer, and inflammation. The principal limitations are the poor oral bioavailability (shared with all comparators except navitoclax), the absence of published definitive clinical trial results in the senolytic indication as of the most recent monograph revision, and the cell-type-dependent variability in senolytic potency.

Investigators considering fisetin for research applications should expect a compound with moderate senolytic potency (less than navitoclax, greater than quercetin alone), broad multi-target pharmacology, a favorable safety profile at doses up to 20 mg/kg orally, and a translational trajectory that is active but has not yet produced definitive Phase 2 or Phase 3 clinical efficacy data.

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